ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL. 7 (O. S., Vol. XII) JULY, 1933 NUMBER 1

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Entered as second class matter at the Post Office, Ann Arbor, Mich.
Application for transfer of entry to Lancaster Pa., Post Office pending

ANNALS OF
INTERNAL MEDICINE

VOLUME 7 JULY, 1933 NUMBER 1

PRESENTATION OF THE JOHN PHILLIPS MEMORIAL PRIZE TO DR. WILLIAM CASTLE

By F. M. POTTENGER, M.D., F.A.C.P., *President, American College of Physicians*

MEDICINE is an unfolding science. Great advances have been made by few; but the real test of our profession is its ability to follow its leaders.

Doctor Castle, it has been your good fortune not only to be a follower in the first ranks, but to push forward into the unknown. Your work on the anemias has added organized knowledge where but a short while ago ignorance blocked our way. Your work has rendered so great a service to Medicine that the Committee on the John Phillips Memorial Prize of The American College of Physicians has designated it worthy of unusual recognition.

We hope that the insight which you have now attained in this important field will enable you to add still more to our knowledge.

Doctor Castle, I take great pleasure in presenting you with the John Phillips Memorial Prize of The American College of Physicians.

THE ETIOLOGY OF PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS*

By W. B. CASTLE, F.A.C.P., *Boston, Massachusetts*

DURING the past five years the problem of the etiology of pernicious anemia and other macrocytic anemias responding to liver extract has been investigated at the Thorndike Memorial Laboratory, Boston City Hospital. At various times Dr. Wilmot C. Townsend, Dr. Clark W. Heath, Dr. Maurice B. Strauss and myself have been engaged in this study. Last year, in collaboration with Dr. C. P. Rhoads of the Rockefeller Hospital, the macrocytic anemia of sprue in Puerto Rico was studied under the auspices of the Rockefeller Foundation. Recently Dr. Strauss has investigated the mechanism of the pernicious anemia of pregnancy.

The technic first employed was the incubation of various preparations of normal human gastric juice with beef muscle and the administration of the suitably prepared incubated material to cases of pernicious anemia. The presence or absence of hematopoietic effects has been determined by the appearance or non-appearance respectively of significant reticulocyte increases during successive ten-day periods of daily administration of the incubation mixtures. Sufficient experiments of this type have previously been reported to demonstrate that Addisonian pernicious anemia is a deficiency disease conditioned by the lack of a specific intrinsic factor, present in normal human gastric juice and absent in that of cases of pernicious anemia in relapse.[1, 2, 3, 4] In the normal individual the function of this intrinsic factor of the gastric juice is to interact with an extrinsic factor in the food to produce specific hematopoietic effects (demonstrable in pernicious anemia). Alone, neither normal human gastric juice nor beef muscle has yielded significant hematopoietic responses in pernicious anemia. However, the daily administration of mixtures of beef muscle and gastric juice to suitable patients with pernicious anemia invariably produced reticulocyte increases and when prolonged over several weeks was sufficient to bring the blood and the clinical condition essentially to normal. The interaction of these two factors may, therefore, be regarded as preventive of the development of pernicious anemia in the normal individual. Conversely, the failure of this reaction to take place may be expected to lead to the development of pernicious anemia. Thus, all the patients with Addisonian pernicious anemia in relapse, who have so far been examined, have shown an inability to carry out this essential reaction. It is important to emphasize that these observations demonstrate the existence of a physiological mechanism in the normal individual which

* Address delivered by Dr. W. B. Castle as recipient of the John Phillips Memorial Prize at the Montreal Meeting of the American College of Physicians, February 6, 1933.

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is absent in the patient with pernicious anemia in relapse. Both the food and the stomach are involved in this process. On the other hand, the demonstration of the hematopoietic activity of various substances such as arsenic, liver, kidney, brain, and even stomach preparations or the injection of milk or gastric juice, does not necessarily establish their etiological relationship to the disease, despite their efficiency in its treatment.

The intrinsic factor of the normal gastric juice has been defined as a heat-labile substance, not corresponding in its properties to hydrochloric acid, pepsin, rennin, or lipase.[5] Recently Dr. Strauss and I have turned our attention to the extrinsic factor, and incubation of various substances has been carried out with normal human gastric juice. Starting with the results of the previous observations demonstrating that the extrinsic factor of the food has been found in the washed proteins of beef muscle precipitated at pH 6, but not in washed casein or wheat gluten, the former of which is a relatively complete protein,[4] the work was extended to nucleoproteins and their derivatives. The results of these observations make it clear that nucleoproteins, and nucleic acid from animal sources and from yeast, cannot react effectively with normal human gastric juice. On the other hand, we have now shown that the extrinsic factor is present in autolyzed yeast in approximately 20 times the concentration found in beef muscle. It is not destroyed by autoclaving for five hours at 15 pounds' pressure, which destroys vitamin B_1 but not vitamin B_2; and it is separable from the proteins of yeast by 80 per cent alcohol in which it is soluble.[6] In addition, the extrinsic factor is found in rice polishings and in wheat germ. Liver extract No. 343 N.N.R., a source of vitamin B_2, may be rendered inactive in pernicious anemia by hydrolysis with dilute sulfuric acid, a procedure that does not destroy vitamin B_2. If this hydrolyzed material is then incubated with normal human gastric juice, it is again rendered active. In general, then, the characteristics and distribution of the extrinsic factor correspond to those of vitamin B_2.

We[5] have previously pointed out that there are three possible mechanisms by the action of one or more of which pernicious anemia may be produced, namely, a lack of the specific intrinsic factor of the stomach, a lack of the extrinsic factor of the diet, or a failure of absorption or utilization of the product of the interaction of the intrinsic and extrinsic factors. These postulates can now be extended to include other types of macrocytic anemia and can be shown to be consistent with the supposition that vitamin B_2 is the extrinsic factor.

1. All cases of classical Addisonian pernicious anemia in relapse which we have studied thus far, have been mainly due to the operation of the first mechanism, a lack of the intrinsic factor in the stomach.

2. Sprue with macrocytic anemia, on the other hand, has been successfully treated by Elders[7] and Ashford[8] with diets rich in animal protein, and hence rich in vitamin B_2; and more recently we[9] have had success in certain cases with yeast. Similarly Wills[10] has successfully treated tropical macrocytic anemia with autolyzed yeast alone, and Vaughan and Hunter[11]

have obtained definite results with the same substance in the macrocytic anemia of celiac disease. These results may now be explained on the basis that in all probability the anemia was mainly due to the second mechanism outlined above, namely, a lack of the extrinsic factor in the diet.

3. It must, however, be remembered that in certain cases of macrocytic anemia, the third possibility, namely, defects of absorption, may be involved. Thus, in certain cases of pernicious anemia and especially in advanced cases of sprue, enormous doses of liver extract given by mouth may be relatively ineffective while the usual parenteral dose gives a typical response.[5] It is possible that various factors within the body may also be involved in these differences. It has also been pointed out that the same mechanism may not always be active. This is best illustrated by certain cases of the pernicious anemia of pregnancy which during pregnancy show no response to beef muscle. After delivery, however, beef muscle produces a reticulocyte response which may be then increased by the addition of normal human gastric juice.[12, 13] This we interpret as indicating a lack of the intrinsic factor in the gastric juice during pregnancy and its partial recrudescence after parturition. The reappearance of the intrinsic factor has also been observed in one case of pernicious anemia following the improvement induced by liver therapy.[5]

It is now possible to explain why certain cases of macrocytic anemia will respond to both liver extract and autolyzed yeast and others only to liver extract. The difference appears to depend on the presence or absence of the intrinsic factor. In the light of this evidence it is clear that the common factor for producing macrocytic anemia is the failure of the specific reaction between the extrinsic and the intrinsic factors. These anemias should, then, occur both where, on the one hand, the diet is deficient in vitamin B_2, and on the other hand, where, although the diet is not grossly deficient, lack of the intrinsic factor is found. Thus, sprue and the macrocytic anemias of the tropics occur in communities or in individuals partaking of defective diets and show gastric anacidity less commonly than is found in patients with Addisonian pernicious anemia, who usually have more normal diet habits. In many cases a combination of gastric defect and dietary deficiency may exist, which would have the same result upon the specific hematopoietic reaction as a total absence of either of its components.

If the evidence be valid that the extrinsic factor of the specific hematopoietic reaction with normal human gastric juice is vitamin B_2, a new concept of the relation of certain vitamins to the conditions caused by their lack would seem to be involved. The action of a vitamin in curing a deficiency may thus be essentially dependent upon a specific process in the gastrointestinal tract; and the deficiency state not so much a deficiency in the diet as a deficiency of a reaction in the gastrointestinal tract or elsewhere in the body.

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STUDIES ON THE FUNCTION AND CLINICAL USE OF CORTIN*

By FRANK A. HARTMAN, PH.D., *Buffalo, New York*

A CAREFUL consideration of the functions of cortin should precede its clinical application.

From a study of clinical material and animal experiments certain functions of cortin are indicated. We propose to discuss these together with findings which may bear on other functions not clearly indicated. The symptoms pathognomonic of Addison's disease—asthenia, gastrointestinal instability and pigmentation—may give us clues to follow in our hunt for the function or functions of cortin. Of these asthenia is outstanding.

ASTHENIA

Usually this is the first symptom to appear. It develops so insidiously that the subject may not be able to date its first appearance because in the early stages it may be attributed to physiologic fatigue or to a slight infection. It may be noticed as an inability to perform the usual tasks without early fatigue. At this time there is no loss in power for single efforts; inability is noticeable only on continued application.

Asthenia of the nervous system may appear quite early. Mental effort quickly brings fatigue. The patient is irritated by stimuli which ordinarily would be tolerated. With progress of the disease, a general debility reduces his activity to a minimum and he develops an inertia toward activity of any sort. Finally he may reach the stage of prostration or coma. Other evidences of involvement of the nervous system are insomnia, mental depression, failure of memory, poor judgment, lack of coöperation; later, heightened motor activity; and in the preterminal stage, twitching and convulsions. That cortin insufficiency is responsible is demonstrated by the disappearance of these symptoms with its administration.

When the patient responds to cortin the symptoms disappear in reverse order. Moreover the stages are better defined during recovery because in a relapse, especially in the late stages, developments may occur so rapidly that some of the symptoms may be absent or missed.

Coma is replaced by a state of heightened irritability as shown by increased motor activity, aimless movements, twitching and marked myotatic response to stimuli. With return of consciousness there may be disorientation, mental irritability, lack of coöperation and sometimes noisiness. The overactivity gives evidence of drive.

* Presented before the Montreal Meeting of the American College of Physicians, February 7, 1933.

From the Department of Physiology, University of Buffalo.

The more recent work in this laboratory was made possible by a grant from the Carnegie Corporation of New York to the Carnegie Institution of Washington.

The next state is one of calm in which twitching and restlessness disappear. Pain is relieved and the patient becomes more rational and sleeps much.

Finally the stage of recovery is reached in which mental alertness returns and asthenia is reduced. The patient sleeps so well that he obtains adequate rest from an ordinary night's sleep. His insight and judgment are greatly improved; he becomes coöperative and takes an interest in his surroundings.

In man these effects begin to appear within a few hours after injection and the recovery stage is usually reached within three days. In animals the changes may be more prompt because relatively larger doses can be administered.

Nervous Asthenia. A careful study of the symptoms seems to show involvement of both muscular and nervous systems. Experimentally this has been shown to be true.

Gans and Miley[1] found that the nerve-muscle preparation from adrenalectomized rats became fatigued more easily than did that from normal rats. Hartman and Lockwood[2] have shown that cortin insufficiency involves the reflex as well as the myoneural junction and the muscle itself. This was proved in doubly adrenalectomized rats with and without cortin treatment. A spinal preparation was made by cutting the cord just below the level of the diaphragm. Fatigue resistance of the reflex arc, myoneural junction and muscle was determined by successively stimulating the opposite sciatic nerve, the sciatic nerve of the same side and the gastrocnemius directly, making the change in each instance at the point of complete fatigue. The same difference in resistance to fatigue was shown in the reflex and myoneural junction as in the muscle itself. That is, cortin increased the resistance about six times in each region.

Objective proof that centers in the cerebrum are influenced by cortin has been obtained by Anderson, Liddell and Hartman (unpublished results). They found that sheep made neurotic by attempting to develop too fine a discrimination in a conditioned reflex were improved by the injection of cortin. The neurotic animals showed frequent spontaneous movements while in the harness. These were absent in non-neurotic animals. Moreover, the response (jerk of the left foreleg) to the conditioned stimulus was of a much smaller magnitude in the former. Under the influence of cortin the neurotic sheep behaved more like normal animals, in that spontaneous movement was much reduced or abolished and the magnitude of the conditioned response was much larger. After about five hours the effect of cortin began to disappear.

Further evidence of cortin effect on the nervous system has been obtained by Hartman, Beck and Thorn[3] in cases not definitely Addison's disease but in which nervous fatigue occurred without evidence of organic neurological change. A surgeon was troubled with fatigue, insomnia, visual disturbance at night, tremor, and pylorospasm whenever exertion was required. He was convinced that cortin was of decided benefit particularly to the nervous system. This was shown by improvement in vision, insomnia, fatigue, tremor, and pylorospasm.

Other cases of widely different type, but in which fatigue was the outstanding complaint, showed definite improvement in the nervous symptoms under treatment with cortin. Mental irritability was decreased, sleep improved and resistance to fatigue, both mental and muscular, was increased. This was not due to suggestion because injections of saline or adrenalin were without effect. Moreover the effect was diminished or absent if the quantity of cortin was too greatly reduced.

In some cases in which definite organic neurological change was accompanied by muscular weakness, cortin caused not only improvement in the motor functions but also a rather striking change in the mental status. Fatigue was diminished with a concomitant increase in strength. Myotonic manifestations and fibrillation, when present, decreased. Depression was replaced by cheerfulness, and a sense of well-being even to the point of euphoria. Irritability disappeared; sleep improved; and erotism became normal in some of the males. These improvements occurred without real changes in the organic neurological state.

Improved motility (in muscular atrophy) may have been brought about by improved strength, diminished fatigue, and increased sense of well-being.

Italian workers [4] have found that cortical extract is beneficial in certain types of neurasthenia and psychasthenia.

Cortin affects the nervous system in normal individuals under certain conditions. If the subject is in excellent condition effects are not easily detected, but if he is below par, e.g. tired or nervous from overwork or recovering from an infection, response to cortin is quite noticeable. In the course of half an hour he becomes drowsy. While the effect lasts he sleeps more soundly and his sleep is more beneficial so that less sleep than usual may suffice. There may be an increased sense of well-being sometimes to the point of euphoria. Later he may become more alert and seem physically more fit. In a nervous or tired subject an increased reserve seems to be acquired. Certain subjects have shown these responses many times.

We have dwelt at length on the evidence of involvement of the nervous system including the higher centers in the action of cortin because this has been somewhat ignored heretofore.

Muscular Asthenia. It is impossible to separate the muscular element from the nervous element except in a muscle preparation. Therefore, any consideration of asthenia in the intact organism involves both the nervous and muscular systems. We have already described experiments which prove that muscle itself is involved in the asthenia.

We [5] have studied the effect of cortin on the resistance of the intact muscles to fatigue. This was measured objectively by means of an ergometer. Positive effects were obtained in widely varying clinical cases and, to a lesser degree, in some normal individuals. Increase in power to work without fatigue was associated with general improvement, although in some instances raising of the fatigue threshold preceded definite subjective sensation of improvement. In a few clinical cases the working power was increased many fold while in normals the increase was only 50 to 100 per cent.

Baird and Albright[6] found no change in resistance to fatigue, as shown by the ergometer, in their cases of Addison's disease under treatment with cortin except that which might be accounted for by practice. Two out of our six cases tested by the ergometer showed no change under treatment.[5] In the others, the increased power to work without fatigue often came several weeks after treatment had been started. The practice factor was ruled out.

Eagle, Britton and Kline[7] found that cortin increased the energy output of normal dogs working on a treadmill up to 100 per cent. However, they do not mention the temperature at which their dogs worked. In the Fatigue Laboratory at Harvard, it has been found that dogs will travel much farther than the best performance obtained by Eagle, Britton and Kline if the surrounding temperature is cool (private communication of Dr. D. B. Dill).

There are many factors undoubtedly involved in muscular asthenia: the nervous factor already mentioned, a circulatory one in some instances, and local changes involving the metabolic activity of the muscle itself. In adrenal insufficiency lactacidogen[8] and phosphagen[9] are reduced. Buell, Strauss and Andrus[10] found that the ability of the gastrocnemius muscle, from adrenalectomized animals, to produce lactic acid autolytically was impaired. Likewise, it has been found that lactic acid formation under different conditions of rest and activity in the muscle of adrenalectomized rats is greatly reduced.[11]

Circulatory Asthenia. The blood pressure is usually lower than normal in an advanced case of Addison's disease. The fundamental cause has not been ascertained. Heart action may be feeble. This may be similar in origin to the weakness found in skeletal muscle. However, there is some evidence that the blood vessels themselves may be at fault. The fall in blood pressure which often occurs when the patient changes from a horizontal to a vertical position may be significant. Lack of vasomotor compensation seems to be involved, which in turn includes reflex mechanisms.

Concentration of the blood together with an increase in the relative volume of erythrocytes, according to Rogoff and Stewart[12] (see also Estrada[13]), can be detected in most cases somewhat in advance of the onset of symptoms. Roughly, this change is coincident with that in the non-protein-nitrogen.

Swingle et al[14] recently found a decline in arterial pressure of 20 to 25 millimeters of mercury in early stages of diminution of blood volume in the dog.

Viale and Bruno[15] in 1927 observed that the viscosity of the blood rose, accompanied by a marked increase in all blood cells, producing mechanical obstruction to the circulation. They suggested that the function of the adrenal was to regulate the proportion of plasma and that loss of plasma was due to increased vascular permeability. Edema of the intestinal mucosa, congestion of the pancreas and spleen, and an increase of water in the muscles were also noted. They attribute the increase of permeability to the nervous system and to changes in vasomotor substances in the blood.

According to Rowntree and Snell[16] (p. 198) a decrease in blood volume occurs only in the terminal stage or in crises of Addison's disease. The lowest volumes were found in shock while improvement was followed by recovery in blood volume.

Compensation for hemorrhage fails in adrenal insufficiency.[17] In animals (rats) which do not develop adrenal insufficiency as easily as cats or dogs, the blood volume may show little or no change. Yet the water content in many of the tissues of the body is modified.

In rats we have found that complete removal of the adrenals causes an increase in the water content of many of the tissues, and this occurs in animals not showing a severe degree of insufficiency (figure 1). The increase is

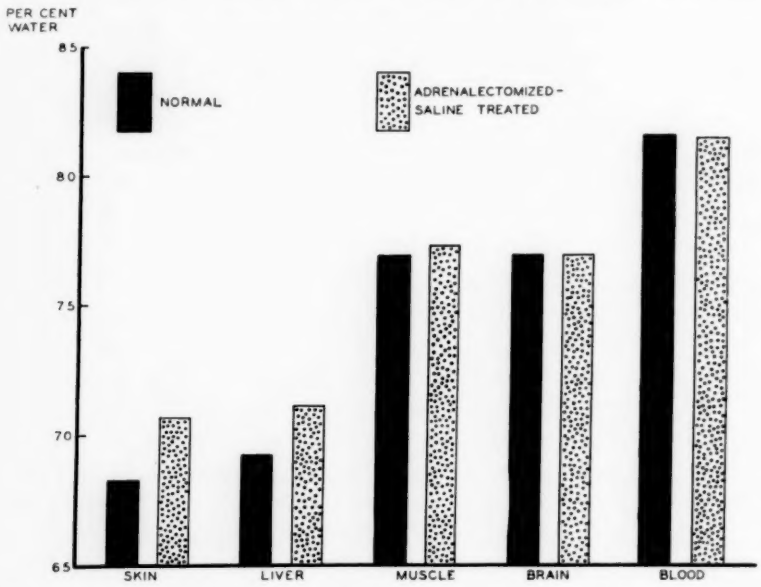

FIG. 1. Water content of tissues in normal (9) and adrenalectomized rats (9) at room temperature (27° C.)

largest in skin and liver, is smaller in muscle and very slight in brain. Blood contains the same water content in both normal and adrenalectomized animals. Exposure of adrenalectomized animals to cold or to heat produces less shifting of the water of the tissues in adrenalectomized untreated animals than it does in normal animals. The injection of cortin increases the ability of the tissues to shift water under such stresses.[18] This would account at least in part for the lowered resistance to heat which adrenalectomized untreated animals possess (figure 2), since much of the heat loss is from evaporation of water (in the rat, from expired air and saliva). The slower shift of water may be due in part to inadequate circulation under stress as well to modified permeability.

Durant[19] found that adrenalectomized rats had an average systolic blood

pressure of 77 millimeters of mercury as compared with 112 millimeters for normal rats. This lower pressure developed several hours after the removal of the glands.

How early definite hypotension occurs in Addison's disease is difficult to determine. So often the blood pressure change is not considered significant until the disease is advanced.

In the shock or coma of Addison's disease it is sometimes impossible to correct the anhydremia by administration of fluid subcutaneously or intravenously. On the other hand, a few hours after administration of adequate cortin the readjustment occurs and anhydremia begins to disappear.[20] At the same time the blood pressure rises. Swingle et al [14] emphasize the inability of cortin-insufficient dogs to take up water from the tissues. They believe the fall in blood pressure to be caused by decrease in plasma volume.

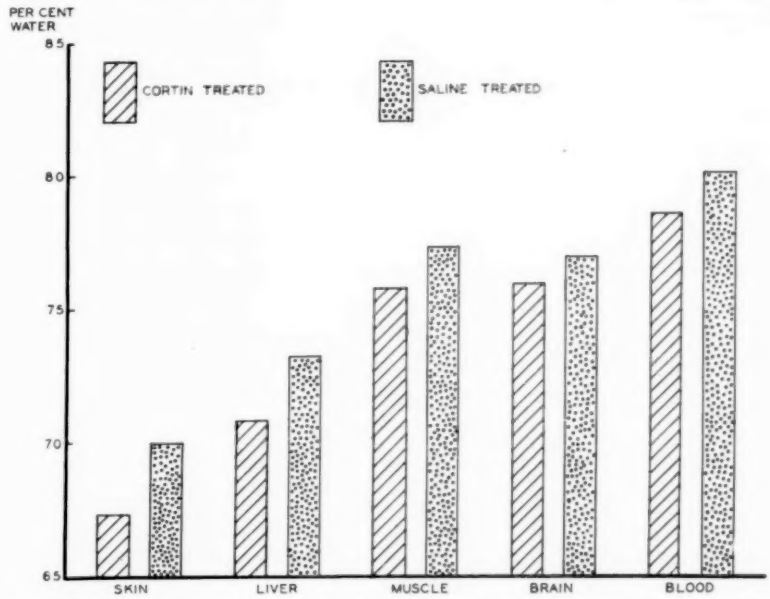

FIG. 2. Water content of tissues in adrenalectomized rats after exposure to 37° C.; one group (7) injected twice daily with 0.5 c.c. of cortin and the other (8) twice daily with 0.5 c.c. of isotonic NaCl solution. The exposure of the NaCl group was for 132 minutes only because of collapse while that of the cortin group was for 191 minutes.

Because cortin does not raise the blood pressure of normal dogs they conclude that it "per se has no effect on blood pressures." This does not follow.

Cortin seems to make the enfeebled heart of an Addisonian patient beat more strongly. It raises the resistance of reflexes to fatigue and thus possibly has an effect on vasomotor tone which in turn influences permeability.

Baird and Albright [6] found that the poor vasomotor response in Addison's disease was improved by cortin. Cortin may also influence the permeability of tissues as our observations have indicated in the water shift in rats.

The influence of cortin on hypotension in cases of Addison's disease is

not in keeping with other improvements, except when the pressure approaches shock levels. Then cortin, if effective, raises the pressure to 75 or 85 millimeters of mercury within two or three days after which there may be a gradual rise to 90 millimeters or more. However, the pressure commonly remains lower than normal, especially in cases of long standing. We have had cases in which the systolic blood pressure rarely rose above 90 millimeters even with long-continued treatment, yet symptoms of asthenia in the nervous and muscular systems had disappeared. Whether this was due to inadequate dosage or to an irreversible change in the circulatory system remains unsettled. The amount of cortin administered was much less in proportion to that given adrenalectomized animals.

Simpson [21] likewise finds that the rise in blood pressure upon treatment with cortin is belated and that the upper limits of blood pressure are subnormal.

Renal Insufficiency

Following the discussion of circulatory asthenia, we take up that of renal insufficiency because of the possible relationship.

We know that cortin is necessary for normal kidney function because if the subject (whether an adrenalectomized animal or a case of Addison's disease) lives long enough this organ begins to fail. Started in time cortin corrects the condition. In some instances the failure may be attributed to faulty circulation. In others further cause must be sought since the blood pressure does not go low enough to account for the disturbance. Moreover the decrease and recovery of kidney function do not run parallel to the blood pressure changes, there being considerable lag.

That the kidney is directly involved in cortin insufficiency seems to have been shown by the work of Hartman, MacArthur, Gunn, Hartman and MacDonald [22] in which it was found that in chronic adrenal insufficiency of cats there was an accumulation of large quantities of lipoid substances in the tubuli contorti.

A more careful study of the kidney in this condition showed degeneration of the convoluted tubules.[23]

Harrop, Widenhorn and Weinstein [24] believe that the diminished nitrogen and urea output, the lessened volume of urine, and the albuminuria produced by adrenal insufficiency indicate a special influence of the adrenal cortex on kidney function.

It seems impossible in view of the facts to account for the influence of cortin on the kidney entirely through circulatory changes.

Gastrointestinal Instability

Some Addisonian patients give a history of very early gastrointestinal symptoms while others experience these symptoms much later. These might be accounted for in part by changes in the nervous system. In the later stages, however, circulatory change is a factor. Not only the more sluggish

circulation associated with hypotension but hemorrhages and ulcers which develop indicate a circulatory basis. Cortin stops nausea and vomiting; appetite reappears and weight is regained. In patients the limited amount of cortin injected probably accounts for the failure to reach the former weight level. Doubly adrenalectomized animals not only regain the former weight but with adequate cortin may go beyond. Indeed, this is a test of the potency of an extract (especially in immature animals). Cortin likewise stops the hemorrhage which sometimes occurs from the alimentary canal in late adrenal insufficiency in animals.

Metabolism

It is well known that cortin is necessary for normal metabolism. Aub, Forman and Bright[25] in 1922 showed that metabolism was reduced after removal of the adrenals. This is due in part to changes in the metabolism of muscle itself since oxidation is nearly always lower in the muscle of adrenalectomized animals.[26] In 1928 we[27] showed that metabolism of adrenalectomized cats could be maintained within normal limits with very small amounts of cortin. Webster, Pfiffner and Swingle[28] in 1931 confirmed our results and showed further that metabolism could be brought back to normal after allowing animals to pass into the late stages of adrenal insufficiency. They were unable to show an increase in metabolism in normal animals after the injection of cortin. These effects on metabolism were independent of the thyroid.

It has recently been demonstrated (Griffith, Winter and Parsons, unpublished) that cortin has no effect on the basal metabolism in normal human beings.

A limitation of ability to increase metabolism to meet the demands of cold has been shown in cortin insufficiency in animals.[29] At first untreated adrenalectomized animals maintain a compensatory heat production when exposed to low temperatures. After a short time, however, this fails, and heat production may even fall below what is normal at room temperature. Adrenalectomized animals treated with cortin are able to compensate by producing the extra heat much as do normal animals (figure 3). This failure to produce heat in adrenal insufficiency on exposure to cold is not due to reduction in the blood sugar because it frequently occurs with normal sugar values. Much of the heat production comes from muscular activity. This is reflexly increased upon exposure to cold. The easy fatigue of the reflexes after adrenalectomy may account, in part, for the failure to produce the extra heat. In addition, changes in the heat producing tissues themselves may be partially responsible.

Growth

Cortin is essential for growth, whether it be the natural development of the young animal or the renewal of tissue in the healing of wounds. In adrenal insufficiency growth or the healing of wounds may even stop. Upon

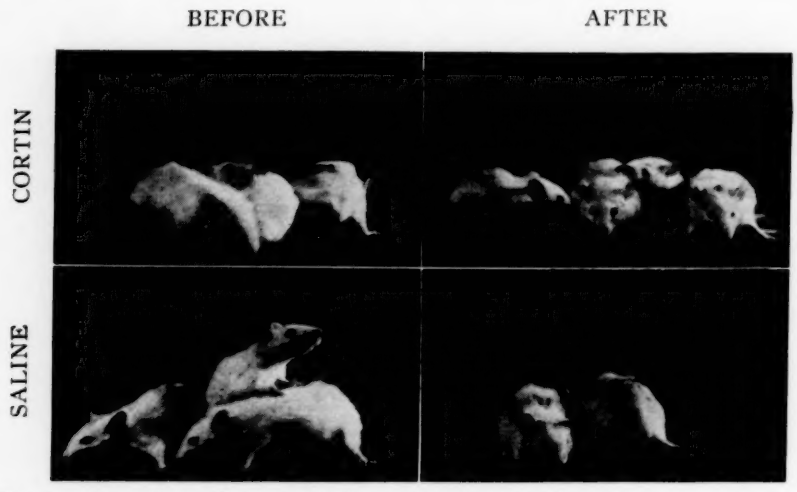

FIG. 3. Adrenalectomized rats before and after 85 minutes' exposure to 4° C.; one group injected twice daily with 0.5 c.c. of cortin and the other twice daily with 0.5 c.c. of isotonic NaCl solution. One NaCl treated rat died.

the administration of adequate amounts of cortin growth is resumed at its former rate. This is also true of the healing of tissues. However, the more extensive the injury the greater the amount of cortin required.

RESISTANCE TO TOXINS

It is well known that in adrenal insufficiency there is a lowered resistance to toxins. It has been shown that cortin increases the resistance of adrenalectomized animals to bacterial toxins.[30, 31] Likewise it has been shown that infections increase the demand for cortin. Adrenalectomized animals which become infected must be injected with considerable amounts of extract in order to recover. Likewise in Addison's disease cases maintained at a constant level with a certain dosage require much more cortin when infections are contracted. Death from a minor infection is not uncommon.

The pathological changes produced in the adrenals from superficial burns[32] indicate the possibility of adrenal insufficiency. In such conditions the symptoms which develop are similar to those in adrenal failure. An illustrative case has come under our observation. A child, five years of age, was severely burned on about 30 per cent of her body surface. On the first day she was nauseated. On the second day she became irrational and delirious at times, and there was considerable muscular twitching and irritability. She could not retain liquids. On the third day, her temperature was subnormal and she was seized with a convulsion, after which she was sent to the hospital. Fluids were injected together with large amounts of cortin and within twenty-four hours she had come out of the semi-comatose condition and showed general improvement. Within forty-eight hours after instituting treatment with cortin and fluids she could retain fluids by mouth and the kidneys were functioning for the first time since the injury. The

response to fluids and cortin was so similar to that obtained in the coma of Addison's disease that we mention it here. The relative parts played by fluid and cortin in the recovery were undetermined.

Relation of Cortin to Vitamin C

Cortin seems to have some function in the utilization of certain vitamins. The changes that take place in the adrenal gland with the development of scurvy indicate possibly an overtax on this gland. The adrenal is rich in vitamin C (hexuronic acid), which (in the guinea pig) is not synthesized to any extent in the body. Therefore its concentration in the adrenal cortex may be significant. We[33] have obtained evidence that cortin aids in the utilization of vitamin C (figure 4). Guinea pigs fed a diet free from this

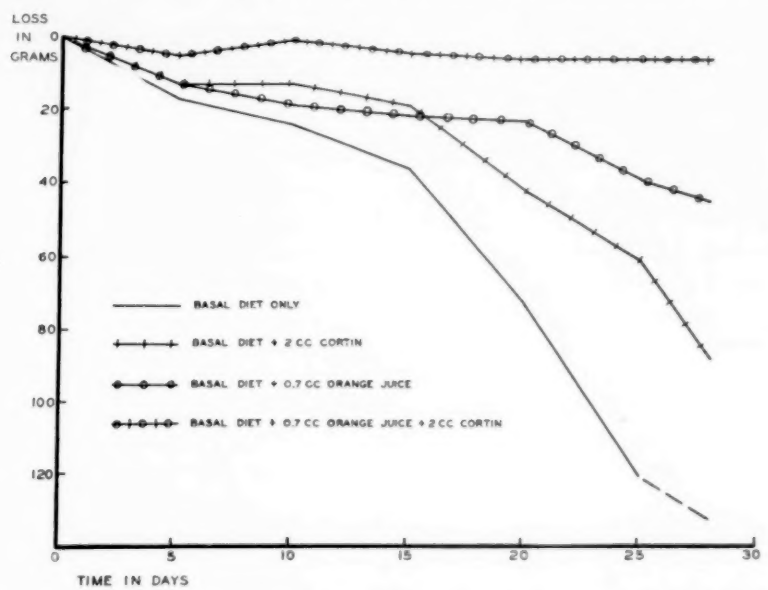

Fig. 4. Loss in weight of guinea pigs on a diet in which vitamin C is absent (basal) or inadequate (0.7 c.c. orange juice) showing influence of daily injections of cortin.

vitamin, if injected with cortin, resist scurvy longer than do similar animals without cortin. This is not due to the presence of vitamin C in the cortin extract for in the preparation extraction by ether eliminates it. If guinea pigs are fed a diet containing added vitamin C in amounts inadequate for maintenance they resist scurvy longer if injected with cortin than do animals similarly treated but with cortin omitted. Their response to cortin indicates a better utilization of the available vitamin C.

Relation to the Gonads

There is a good deal of clinical evidence of an intimate connection between sex characters and the adrenal cortex. Tumors of the adrenal body

are sometimes associated with precocious development of the reproductive organs. Hyperplasia of the adrenal gland may be associated with pseudohermaphroditism especially in the female. In the latter case the male primary and secondary sexual characters tend to increase at the expense of the female.[34]

In Addison's disease menstruation may cease and libido in both sexes may diminish or disappear. These may not be direct effects of cortin insufficiency since they could be explained by the lowered activity of the organism generally. Cortical extract may cause the return of menstruation and frequently libido is increased.

Various adrenal preparations have been found to influence the development of the gonads.[35, 36]

Atwell [37] has found that the ovaries of hypophysectomized tadpoles become larger in animals treated with extract containing cortin than in untreated controls. This observation indicates that the action is not through the pituitary.

It has been shown that the interval between menstrual periods can be shortened three to five days in normal women by the injection of cortical extract.[38]

Pregnancy increases the demand for cortin except in the dog. Elliott and Tuckett [39] found that a cat near full term died more speedily after complete adrenalectomy than similarly operated cats not pregnant. In rats we find that pregnancy requires more cortin.

A condition in the human suggesting adrenal insufficiency sometimes develops in pregnancy. In one case of this kind, treatment with cortin resulted in striking improvement.[40]

Whether or not cortin alone is responsible for these influences on the sex organs or whether cortin is merely necessary for the well-being of the rest of the organism, thus indirectly influencing the gonads, while a second hormone affects the gonads directly, remain to be settled.

Pigmentation

Although pigmentation is considered one of the cardinal signs in Addison's disease, it is not always present.[41] Even where pigmentation is present it is sometimes impossible to attribute it to Addison's disease because of the similarity to the pigmentation found in other conditions. In four of our cases definite decrease in pigmentation has been shown after the use of cortin.

It is interesting to note that after recovery from a relapse in a severe case of Addison's disease, desquamation over the body may become very marked. In adrenalectomized animals, on the other hand, no proved changes in pigmentation have ever been recorded. There is a change in the skin itself, however. A freshly shaven area in a white cat becomes dirty gray and appears poorly nourished. In the late stages of insufficiency the hair falls out easily, or can be pulled out in masses. Administration of cortin to these animals restores the skin to its healthy appearance and the hair again becomes fixed.

Chemical Changes in the Organism

It has been thought that a change in some one substance in the body might account for cortin insufficiency. Many chemical changes have been suggested as responsible. We shall briefly discuss two.

Carbohydrate Metabolism. Although it has been known for a long time that the blood sugar was frequently low, especially in the later stages of adrenal insufficiency, no great significance was attributed to this by any one until Britton,[42] on the basis of certain experiments, concluded that the change in carbohydrate metabolism in adrenal insufficiency was of outstanding importance. Undoubtedly, it is important in many instances, yet the irregularity of its appearance, even in severe cases of insufficiency, would seem to rule it out as the chief effect of adrenal insufficiency.[18]

Sodium and Potassium. The loss of sodium and the increase in potassium in some instances of adrenal insufficiency likewise suggested a fundamental cause. Baumann and Kurland[43] observed a fall in sodium and a rise in potassium of the plasma after adrenalectomy in cats and rabbits. Loeb[44] has found similar changes in patients with Addison's disease. Marine and Baumann[45] were able to show that the administration of isotonic solutions of sodium compounds increased the duration of life in adrenalectomized animals. This has been confirmed by a number of workers. The injection of large amounts of isotonic solutions of sodium compounds probably helps to restore the water exchange in tissues. Such injections in adrenalectomized rats increase the ability to form anti-bodies.[46] Anti-body formation is subnormal in these animals after adrenalectomy.

None of the changes suggested seem to be specific either as a test for adrenal insufficiency or as a primary cause of the condition.

Clinical Use of Cortin

In order to understand better the clinical use of cortin, let us recapitulate the changes which occur in cortin insufficiency: first and foremost, the asthenias of the nervous system, muscular system and circulation, no one of which is very clearly set apart from the others; renal insufficiency, which may be due in part at least to changes in the kidney itself; gastrointestinal instability, which may have both peripheral and central elements; reduced metabolism and growth, which depend upon the activity of the tissues concerned as well as the general body condition; lowered resistance to toxins, which may be merely another aspect of lowered function in a number of tissues; the increased pigmentation and changes in the skin; and the reduced activity of the sex organs. We speak of these as cortin insufficiencies because this substance is able to correct or abolish them. The relationship to vitamin C deficiency likewise must not be forgotten. At the present time the most reasonable hypothesis seems to be that cortin is a general tissue hormone; but, if for no other reason than the importance of the tissue involved, cortin seems to play a paramount rôle in the function of the nervous system.

With an understanding of the changes that take place in the various

stages of adrenal insufficiency and their responses to treatment with cortin, one has a basis for its clinical use in Addison's disease or any other cortin deficiency.

In the early stages of Addison's disease, or in cortin insufficiency in other clinical conditions, there is no criterion for diagnosis. A therapeutic test with cortin seems to be the only means at our disposal to detect the insufficiency. However, a positive response does not necessarily indicate cortin insufficiency since cortin has a pharmacological action in normal subjects.

Conditions for Its Use. Asthenias which are unaccounted for by any known cause can be treated with cortin without harm. So far, no one has been able to show deleterious effects in any organism from the use of cortin. It is only when extracts are crude or toxic that care must be taken. One must bear in mind that the responses from cortin are not necessarily immediate. Although they may occur within a few hours, greater effects may appear after two or three days' treatment and sometimes the most marked effects come several days after treatment is discontinued.

It is best to inject once or twice daily for a week or two and then discontinue treatment. This seems to be more effective than occasional treatment every few days. Moreover, it gives a better test of the possibilities of response in the individual.

We have used cortin in a great variety of conditions—and in considerably more than sixty cases. Many others also have employed cortical extracts which undoubtedly contain cortin, the vital hormone of the adrenal cortex.

Although the benefit which is sometimes derived from the use of cortin may at first suggest that the course of the disease has been checked, such improvement may have to be attributed merely to the pharmacological effects of the extract; namely, improvement of the nervous system, better sleep and an increased sense of well-being even to the point of euphoria. Usually such effects are only temporary. Therefore, too much must not be expected when a positive response is obtained.

Dosage can be determined only by trial, but three to ten cubic centimeters per day of a potent extract (the product of 30 gm. of cortex to each cubic centimeter) should give a positive result in any but severe cases, especially if the treatment be continued for four or five days.

Treatment of Addison's Disease. In known cases of cortin insufficiency, such as Addison's disease, due regard should be given to the conditions which increase the demand for cortin in order to avoid them.[38, 47] These are infections, toxins, exposure to heat and cold, dehydration, strenuous exercise, worry; indeed, any stress which taxes the organism. In normal animals evidence of increased activity in the adrenals under stress is found in their enlargement (table 1).

Treatment with cortin may be intermittent in mild cases of Addison's disease, the dosage being determined by trial. The amount injected daily, small at first, is gradually increased until a response is obtained. It is well

TABLE I

Influence of Various Stresses on Adrenal Weight

	Stress	No. of rats	Adrenal weight Per cent gain over controls	Cortex Per cent gain	Medulla Per cent gain
I.	Exercise	12	14.29	9.2	19.0
II.	Cold	42	10.90		
III.	Trauma	12	5.45		
IV.	Toxin	12	22.90	38.0	23.8

I. 1200 meters in two hours five days a week until 12 exercise periods had been run.
II. Exposed to cold 20 to 75 hours in from 3 to 14 days.
III. Small piece of tail or skeletal muscle removed twice a week for five weeks.
IV. Injected daily with dead *Staphylococcus aureus* for 30 days increasing from 5 billion, first week to 25 billion, last week.

to maintain treatment for a few days until the patient seems to have reached an optimum when treatment may be discontinued for a period. With each sign of cortin insufficiency it is best to resume treatment immediately because the patient tends to go a little farther down hill with each exacerbation. Subcutaneous injection is preferred because of the slower absorption and the ease of accomplishment. The intravenous route is employed in emergencies.

In more severe cases continuous treatment seems on the whole desirable because one is substituting cortin for adrenals that are entirely inadequate. One must also bear in mind that the stage of irreversibility may be unexpectedly reached.

Irreversibility. In the terminal stage of Addison's disease cortin sometimes fails to bring about recovery. This might be due to inadequate dosage or to the development of an irreversible condition. That the latter is sometimes true is indicated by the work of Hartman and Winter.[48] They found sometimes that doubly adrenalectomized animals (cats, guinea pigs and monkeys) that had developed a crisis spontaneously or as a result of exercise, could not be more than temporarily benefited by the administration of large amounts of cortin. This stage of irreversibility seems to vary in different individuals and may develop with few premonitory symptoms. It seems to develop more readily under stress, e.g. toxins and exercise. Repeated relapses to the point of prostration seem to make recovery more difficult. Death may occur suddenly with little warning. Patients suffering from Addison's disease sometimes die under treatment with cortin because exacerbation of symptoms is not accepted as indicating that increased dosage should be speedily instituted. Bearing these points in mind, we find it good practise to inject cortin immediately upon exacerbation of symptoms. The patient is carefully watched and if improvement is not shown within two hours additional injections in increasing amounts are made until improvement occurs. The dosage and frequency may then be gradually decreased as long as the optimum condition of the patient is maintained.

SUMMARY

1. An account of the possible functions of cortin is given to serve as a basis for clinical use of the hormone.

2. The foremost symptoms of cortin insufficiency are asthenias of the nervous, muscular and circulatory systems. The effects of cortin on these systems indicate a paramount rôle in their functions. Because of the commanding place occupied by the nervous system in the organism the function of cortin in its activity is outstanding.

3. In addition, cortin seems to play a rôle in the activity of other tissues including the kidney, gastrointestinal system, and the gonads.

4. General aspects of the problem are the influence on metabolism, growth, resistance to toxins, and changes in the skin and mucosa.

5. A newly discovered function of cortin is the part that it seems to play in the utilization of the antiscorbutic vitamin. Guinea pigs fed a diet deficient in the latter, resist scurvy longer if injected with cortin than do similar animals without cortin.

6. Thus far, none of the chemical changes suggested seems to be specific either as a test for adrenal insufficiency or as a primary cause of the condition.

7. The use of cortin in Addison's disease and other clinical conditions in which asthenia is an outstanding symptom is discussed.

8. The danger of the development of an irreversible stage in severe cases of adrenal insufficiency is stressed.

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DIFFERENTIATING SOME FUNCTIONS OF THE ANTERIOR PITUITARY HORMONES*

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About twenty different physiological effects have already been found to follow the ablation of the anterior pituitary, or to appear in response to supplements of this tissue or its extracts when injected into intact animals. Some of those who have described such effects have wisely refrained from the conclusion that a particular effect necessarily represents a direct and specific response to an anterior lobe hormone. During the years ahead of us the number of truly direct and specific effects, as well as of others of quite secondary and non-specific nature, may be expected to multiply.

In much that I may venture to say on this somewhat inaccessible field of study I speak with no air of finality; also, I must beg permission to mention only half of this group of responses, and to discuss only four of them. The great difficulty confronting investigation in this field is that we are not yet sure that all of the anterior lobe hormones have been isolated or recognized, and that none of those now known has been isolated in absolutely pure form. Indeed, as this paper must indicate, practically all of the preparations hitherto used can be shown to be mixtures containing two or more hormones in addition to other foreign substance.

Clinical studies provided early and numerous instances of functions or functional disturbances associated with the anterior pituitary. The ablation of the pituitary of the immature frog and mammal, and also that of man—work with which the names of P. E. Smith, B. M. Allen and of Cushing are so much associated—resulted in much basic information as to the rôle of this organ in development, in maturity, and in disease. Together with the repair effected by later anterior lobe supplements the responses of the young to hypophysectomy made it clear that this organ contributes something essential to body growth and to the *development* of the sex organs (gonads), the thyroid, and the adrenal cortex. These are four responses with which sound thinking concerning the functions of the pituitary may well begin.

From a different approach to this question a real advance has been made in the detection of the number and types of hormones produced by this gland. Evans and Long[1] disclosed a growth hormone. Smith[2] and Zondek and Aschheim[3] simultaneously certified the existence of a sex maturity or gonad-stimulating principle. The complete distinctiveness and unrelatedness of those two hormones—growth- and gonad-stimulating—has been sharply questioned by Evans, Meyer and Simpson,[4] but the experience of our own laboratory leaves us nearly or quite convinced of their complete individuality.

Much has been written recently concerning a "luteinizing" hormone of

* Paper read at a general session of the Seventeenth Meeting of the American College of Physicians, Montreal, February 7, 1933.

From the Station for Experimental Evolution, Carnegie Institution.

anterior pituitary origin. I believe that the evidence adduced is wholly inadequate, and that the phenomena of luteinization rest upon an explanation which we shall attempt to give elsewhere.

We now turn to a consideration of two specific responses, and of a new and third pituitary hormone. That something contained in the anterior pituitary is responsible for activating the developed mammary gland to the secretion of milk was shown by Stricker and Grüter [5, 6, 7]; this result has been confirmed by Corner [8] and others. Again, Riddle and Braucher [9] showed that the development and secretion of the crop-gland in pigeons is also a specific response to one or another hormone of the anterior pituitary. Quite recently Riddle, Bates and Dykshorn have been able to demonstrate the presence of a hitherto unrecognized hormone of the anterior lobe, and to show that the lactation and crop-gland responses are wholly ascribable to this third pituitary hormone. This new hormone we have called "prolactin." Since the two above-mentioned responses are so clearly dependent on this new hormone, and the description of these points is only now in press, or has appeared only in preliminary notices (Riddle, Bates and Dykshorn [10, 11, 12]), I must here give considerable attention to this aspect of the subject. In doing this we shall incidentally find clear proofs that some of the most currently used pituitary extracts are mixtures of two or three distinct hormones.

In the tabulations which follow we are obliged to give only condensed and rather smooth parts of the voluminous data of Riddle, Bates and Dykshorn, who have used more than 600 animals for these tests. The data of table 1 show that the two types of preparation of "growth" hormone used also contained very considerable amounts of the gonad-stimulating hormone, since the testes of all treated animals show a marked increase in size.* That the preparations did, in fact, contain the "growth" principle is indicated by the rapid and consistent increase of body weight in treated animals. That some of these preparations did, while others did not, contain prolactin is shown by the weights of the crop-glands. We find that an unstimulated single crop-gland of an immature ring dove weighs less than 200 milligrams, and that weights in excess of that amount indicate the presence of prolactin. The greater the amount of prolactin used the greater is the increase of weight in the crop-gland. The duration of the dosage is another factor in this response; we find the maximum weight increase in this gland is attained at the end of seven days; dosage during either longer or shorter periods probably yields less than the maximum response.

Our own preparations of the gonad-stimulating (or sex maturity) hormone cause good testis growth, loss of body weight, and no crop-gland response. They are therefore free from prolactin, and apparently contain little or none of the growth hormone. Prolonged dosage with this hormone causes disproportionately heavier testes (Riddle [13]) than does a shorter term

* A preliminary test of a preparation of the growth hormone of Collip, Selye and Thomson has indicated that it is quite free of demonstrable amounts of the gonad-stimulating hormone; this gives their preparation a wholly unique position among those now available for our tests.

TABLE I

The Hormones Present in Various Anterior Pituitary Extracts, as Determined by Injection into Immature Male Ring Doves (Excerpt from Data of Riddle, Bates and Dykshorn)

Dosage				Age of bird	Body weight		Testes		Weight single crop-gland
Preparation		Per day	Duration		Start	End	Test animal	Average control	
Kind	No.								
		cc.	days	mos.	grams		milligrams		mgms.
Growth hormone	36	0.4	5	3.3	142	170	61.7	13.9	140
(of Lee and Schaffer)	00	0.5	4	2.5	155	168	43.1	6.7	218
Growth hormone	—	0.4	8	2.8	150	173	50.5	8.5	245
Phyone (Van Dyke)	—	0.8	7	2.8	161	193	50.7	8.5	230
Gonad-stimulating*	30	0.5	5	2.7	153	140	43.0	7.6	175
(our own preparations)	43	0.5	5	2.7	160	148	70.4	7.6	150
"Luteinizing" (Method Hisaw et al) (our own)		0.5	7	2.9	174	165	86.2	8.7	780
Antuitrin 2966759 (Parke, Davis Co.)		0.2	4	2.5	157	148	16.2	6.7	185
095029-B		0.3	9	2.7	132	132	67.0	7.6	160
Prolactin (our own)	11a†	4‡	4	2.6	145	146	15.3	7.0	290
	23	10	4	2.6	148	154	7.5	7.0	985
	29	10	5	2.1	164	162	3.9	6.0	880
	34	10	5	2.4	137	118	3.0	6.8	840
	41	4	4	2.5	135	140	6.8	6.7	410

* Traces of posterior lobe hormones present.
† This preparation (11a) contaminated with traces of gonad-stimulating hormone.
‡ Prolactin dosage is expressed in milligrams; usually 0.4 or 0.5 c.c. of fluid was used.

of dosage. The "luteinizing fraction" of Fevold, Hisaw and Leonard[14] is clearly a mixture of gonad-stimulating and prolactin hormones. Commercial antuitrin (Parke, Davis and Co.) contains only the gonad-stimulating (and thyroid-stimulating) principle in amounts demonstrable in our animals. Our preparations of prolactin are shown to be free of the gonad-stimulating hormone; they should contain little or no growth hormone; and they cause marked enlargement and functioning ("crop-milk" secretion) of the crop-glands.

In table 2 it can be seen that lactation in guinea pigs and rabbits is produced by only those particular preparations which in table 1 produced the crop-gland response. Growth or gonad-stimulating hormones fail to activate the mammary gland to the secretion of milk. The new hormone, prolactin, accomplishes this specific activation in normal and castrate females, and even in suitably prepared normal and castrate males (Riddle, Bates and Dykshorn[10, 11, 12]).

Two additional responses, liver and thyroid enlargement, the latter thought to be a specific response to a principle contained in the anterior

TABLE II

Showing that Milk *Secretion* in Guinea Pigs and Rabbits Results from the Injection of Prolactin and Not from the Other Two Anterior Pituitary Hormones (Excerpt from Data of Riddle, Bates and Dykshorn).

Kind and condition of animal	Body weight	Pituitary derivative			Result; including date of beginning lactation
		Type or description	Number	Daily dosage	
	grams			c.c.	
		Guinea pigs			
♂, young (RW)*	393	Prolactin	23	1.0	Lactation 4th day
♀, parous (13)	748	"	29	2.0	Lactation 3rd day
♀, " (2)	645	"	34	2.0	Lactation 3rd day
♂, castrate (R.S.)*	490	"	41	2.0	Lactation 5th day
♀, parous (4)	530	Growth (+ matur.)	00†	1.0	No lactation (6 days)
♀, parous (5)	558	" "	00	1.0	" " (6 days)
♀, parous (11)	810	Maturity‡ (own)	30	3.0	No lactation (8 days)
♀, " (15)	660	" "	30	3.0	" " (6 days)
		Rabbits			
♀, mature (10)	3400	Prolactin	29	3.0	Lactation on 3rd day
♀, castrate (AJ)	3100	"	34	2.7	Lactation on 3rd day
♀, castrate (Gr.)	3700	"	41	4.0	Lactation at 3½ days
♀, mature (Ep)	3000	Growth (+ matur.)§	—	1.4	No lactation (6 days)
♀, mature (22)	3600	" "	—	3.0	" " (10 days)
♀, mature (3)	3300	Maturity‡ (own)	30	3–6	No lactation (6 days)
♀, mature (P)	5400	" "	43	8.0	" " (4 days)

* Preliminary treatment for mammary growth with theelin and progestin.

† The preparation of Lee and Schaffer.

‡ Used as a synonym for the "gonad-stimulating" hormone, and contains traces of posterior lobe hormones.

§ Phyone, prepared by the Wilson Laboratories, method of Van Dyke and Wallen-Lawrence.

pituitary, will next be considered. At least a tentative examination of these responses is possible on the basis of such separation and classification of anterior lobe hormones as is provided by the data of table 1.

Smith and Engle[15] noted that the livers of immature rats given pituitary transplants for periods longer than four days were apparently significantly enlarged. The restoration or repair of the thyroid in hypophysectomized tadpoles had long before been observed after parenteral administration of pituitary by Allen[16] and the Smiths.[17] Otherwise, Riddle and Flemion[18] were first to report that aberrant thyroids and livers result from (the glycerin extract and suspension of) pituitary tissue repeatedly administered (intraperitoneally) to full grown animals (doves). Riddle and Polhemus[19] showed that an extract (beef) prepared for a high concentration of the growth principle, and another (sheep) prepared for high concentration of the gonad-stimulating principle (but each doubtless containing the other, in addition to other anterior pituitary derivatives) both markedly and regularly produced enlargement of the livers and thyroids of young doves and pigeons

of both sexes. Apparently no other studies have reported a response in the liver from anterior pituitary administration; but Putnam, Benedict and Teel[20] produced in dogs a general body overgrowth with which they report an associated general macrosplanchnia. Tables 3 and 4 provide further

TABLE III

Liver and Thyroid Response in Ring Doves Obtained from Hormones (or Preparations) of the Anterior Pituitary (Excerpt from Data of Riddle, Bates and Dykshorn)

Preparation		Daily dosage			Body weight		Age	Liver		Thyroid		Crop-gland active (+) or not (−)
Kind	No.	Volume	Mgm.	Duration	Start	End		Test	Control (an av.)	Test	Control (an av.)	
		c.c.		days	grams		mos.	grams		milligrams		
Growth (+ maturity) (Lee and Schaffer)	36	0.2	1.5	5	139	144	3.1	6.32	2.0–4.0	21.9	14.8	−
		0.2	1.5	5	113	113	3.0	4.43		42.0	20.0	−
		0.3	2.2	9	137	146	3.2	6.12		65.9	20.0	−
		0.3	2.2	10	142	170	3.3	10.06		36.5	14.8	−
		0.6	4.5	9	134	153	3.3	7.80		37.5	(14.1)	−
		0.6	4.5	10	128	134	3.3	6.51		67.0	(26.4)	−
Growth (+ maturity) (traces Prolactin) Phyone (Van Dyke)		0.4	(4)	6	172	182	14.0	10.06	2.0–4.0	41.5	15.3	(+)
		0.4	(4)	7	160	174	14.0	12.05		41.7	15.3	−
		0.8	(8)	5	137	138	2.8	4.42		29.3	13.9	(+)
		0.4	(4)	8	152	164	2.8	4.21		22.3	13.9	(+)
		0.4	(4)	8	150	173	2.8	5.81		44.3	15.3	(+)
		0.8	(8)	7	161	193	2.8	6.00		39.8	15.3	(+)
Gonad-stimulating (+ traces Pituitrin) (own preparations)	36a	0.2	?	5	134	127	2.8	2.15	3.03	26.4	20.3	−
		0.2	?	5	144	136	2.8	2.67	3.03	28.4	20.3	−
	56	0.5	2.2	6	157	141	2.9	2.91	3.33	29.2	20.1	−
		0.5	2.2	6	160	144	3.3	2.44	2.95	52.0	(23.0)	(+)
	43	0.5	3.5	5	143	139	2.9	2.63	2.87	43.9	20.0	−
		0.5	3.5	5	143	130	2.9	2.71	2.87	72.9	20.0	−
		0.5	3.5	5	160	148	2.7	2.62	2.60	24.7	15.3	−
		0.5	3.5	7	172	166	13.7	3.05	2.79	60.8	13.9	−
		0.5	3.5	8	165	162	12.3	2.98	2.95	61.8	(23.0)	−
Prolactin (own preparations)	11a*	0.4	4.0	4	145	138	2.8	3.07	3.33	14.8	20.1	++
		0.4	4.0	4	145	146	2.6	3.25	3.35	36.2	26.2	++
		0.5	10.0	4	152	164	13.5	6.85	3.32	25.2	(14.1)	+++
		0.5	10.0	4	145	146	2.7	3.51	3.35	30.0	26.2	+++
		0.5	10.0	4	132	133	2.8	4.05	3.33	12.7	20.1	+++
	69	0.5	10.0	4	181	162	2.8	3.42	3.07	10.5	(14.1)	++
		0.5	10.0	4	116	110	3.0	2.88	2.87	22.9	20.0	++
		0.5	10.0	7	137	134	3.1	3.07	2.87	10.7	20.0	+++
		0.5	10.0	7	152	137	2.9	3.16	3.02	13.5	(11.9)	+++

* Traces of gonad-stimulating hormone in preparation No. 11a.

data concerning this response of the liver—a response which indeed may be non-specific and of mixed and secondary origin. Our earliest indication of a size increase in the thyroid from something contained in the

anterior pituitary extracts has been fully confirmed and developed much further by others. Loeb and Bassett,[21] Aron[22] and others got thyroid hypertrophy in mammals, with definite evidence for increased thyroid function. Schockaert[23] supplied similar evidence from the duck.

The next step to be taken—and the one undertaken in the following paragraphs—is to identify the particular anterior pituitary hormone responsible for liver enlargement and for thyroid enlargement. On this point it should be noted that an early and remarkable study of Smith and Smith[24] clearly indicated that the pituitary principle that reacts with the endocrine system is separate (even topographically) from that controlling body growth. This view was supported by Evans.[25] Later, Smith[26] supplied cogent evidence for the view that *two* anterior pituitary hormones affect thyroid structure and activity; one—apparently the gonad-stimulating—stimulates the thyroid, while the other—the growth hormone or another one associated with it in the earlier prepared alkaline extracts—depresses the thyroid. Crew and Wiesner,[27] from observations on batrachians, found it probable that there is a separate and distinct thyreotropic hormone. Aron[28] inclines, though with some reserve, to the view that it is the gonad-stimulating hormone that induces the response in the thyroid. Loeb[29] from extensive studies on guinea pigs, concludes there is no connection between gonad growth and thyroid hypertrophy, but a tendency of certain anterior pituitary preparations simultaneously to inhibit full follicular growth, produce lutein bodies, interstitial glands and hypertrophy of the thyroid. The uncertainty and contradictions expressed above are traceable, I believe, to two sources; namely, to the mixed and largely unknown hormone content of the extracts necessarily used hitherto, and to the unsuitability of the rodent ovary for the assay of the gonad-stimulating hormone in unpurified *extracts* (not implants) of the pituitary.

The data of table 3 show that the growth hormone of Lee and Schaffer and that of Van Dyke and Wallen-Lawrence (phyone) gave good increases in body weight in our tests. Our complete assays of these preparations show that they contain the gonad-stimulating hormone in addition to that for growth. One preparation of Lee and Schaffer was free of prolactin, while phyone contains traces of prolactin. The tabulated data show that both preparations cause prompt enlargement of both the liver and the thyroid; to this there is no exception. All of the liver responses shown here were caused by extracts rich in *two* potent hormones which probably never coexist in such quantity in a normal animal. The response may therefore be definitely pathological, not physiological.

Let us next note the effects of some quite good preparations of the gonad-stimulating hormone prepared in collaboration with Dr. Bates in our own laboratory. The injection of these preparations causes our animals to lose weight and, in the quantities used by us, they show no prolactin. They are indeed known to be contaminated with the posterior lobe hormones, but dosage with these latter hormones (alpha and beta hypophamine) was earlier

shown (Riddle and Polhemus[19]) to cause enlargement in neither the liver nor the thyroid of these animals. The data tabulated here show that these preparations of the gonad-stimulating hormone did not (in any case) cause enlargement of the liver; on the other hand, they did (in every case) produce an enlargement of the thyroid. It would seem therefore that the thyreotropic response is produced by the gonad-stimulating hormone, or by another substance (not growth hormone and not prolactin) with similar solubilities. Further, that the liver enlargement is mediated by the growth hormone, or by a substance (not gonad-stimulating hormone and not prolactin) whose solubilities are similar to those of the growth hormones, or—more probably—by growth hormone admixed with non-physiological and incompatible amounts of another pituitary principle or substance. Possibly the same applies to pituitary-induced glycosuria (Houssay and Biasotti[30]).

Examining next the data obtained from similar injections of preparations of prolactin (free or nearly free of the gonad-stimulating and growth hormones) we note that this hormone—though producing its normal effect on the crop-glands and lactation—fails to produce significant size-change in either the liver or the thyroid. These data make it improbable that prolactin alone is responsible for either the liver or thyroid enlargement which so commonly follows the injection of extracts of the anterior pituitary.

Members of the medical profession will perhaps have a special interest in the data of table 4. It is here shown that prolan (from pregnant urine) in the form of antuitrin S, and as generously supplied to us by Dr. Oliver Kamm, of the Research Laboratories of Parke, Davis & Co., does not demonstrably affect the size of either the liver or the thyroid in our animals. I believe that the clinical value of this substance is beyond question; that to ascribe to it a pituitary origin is a most hazardous venture; and that to confuse or to associate it with a gonad-stimulating pituitary principle is a serious error.

The additional data given in the lower part of this table show that the commercial product, antuitrin (Parke, Davis & Co.), causes no enlargement of the livers of our animals; it does, however, in all these tests, cause enlargement of their thyroids. It was earlier shown (Riddle and Polhemus[19]), and is now confirmed, that fresh samples of antuitrin stimulate testis growth in doves and pigeons. Birds injected with this preparation tend to lose weight; their crop-glands are unaffected; but their gonads grow and their thyroids enlarge. Thus we here again find the thyroid response associated with the gonad-stimulating effect.

Summary

Following the isolation of a third anterior pituitary hormone (prolactin) in fairly pure form, together with the marked advance in the assay and purification of the growth and gonad-stimulating hormone facilitated by this accomplishment, it is perhaps admissible to attempt the association of certain tissue responses with each of the (three) now known hormones of

TABLE IV

Liver and Thyroid and Other Responses of Ring Doves to Other Anterior Pituitary and Pregnant Urine Preparations (Excerpt from Data of Riddle, Bates and Dykshorn)

Preparation	Daily dosage			Body weight		Age	Liver		Thyroid		Crop-gland active (+) or not (−)
Kind	Volume	Mgm.	Duration	Start	End		Test	Control	Test	Control (an av.)	
			days	grams		mos.	grams		milligrams		
Prolan (from urine)	0.2	2.0	5	143	140	3.0	3.88	2.0–4.0	21.6	14.8	−
Antuitrin S	0.2	2.0	7	164	159	21.2	4.12		14.1	14.0	−
(095029-B)	0.2	2.0	7	150	148	2.9	3.71		16.8	(21.7)†	−
(Parke, Davis	0.2	2.0	7	156	147	2.8	2.86		25.7	(21.7)	−
Co.)	0.2	2.0	7	147	155	8.0	3.67		13.4	(21.7)	−
	0.2*	2.0	7	132	131	19.2	2.84		18.6	15.6	−
	0.2*	2.0	7	172	162	18.3	3.05		20.7	(22.7)	−
	0.2*	2.0	7	150	145	25.2	4.12		14.5	14.0	−
	0.2*	2.0	7	138	134	19.4	2.60		11.2	(14.3)	−
	0.2	2.0	10	157	140	12.9	5.59		28.0	14.8	−
Antuitrin‡	0.2	2.0	4	157	148	2.5	2.23		11.9	13.8	−
(Parke, Davis	0.33	4.5	4	129	121	3.2	2.09	2.0–4.0	17.3	15.1	−
Co.)	0.25	3.5	5	139	136	2.8	3.91		23.1	(14.1)	−
	0.5	7.0	5	145	129	2.6	2.10		21.9	20.3	−
	0.5	7.0	5	154	137	2.7	2.78		33.3	20.0	−
	0.5	7.0	5	150	141	2.9	2.63		42.4	(26.4)	−
	0.33	4.5	9	124	123	2.7	3.31		35.8	20.0	−
	0.33	4.5	9	120	120	2.7	3.62		24.6	(23.0)	−
	0.33	4.5	9	132	132	2.7	2.84		19.6	14.7	−
	0.33	4.5	9	144	141	2.8	4.68		38.2	20.0	−

* These from preparation No. 095170-A.

† Parentheses indicate control weights which are definitely less reliable than others.

‡ Antuitrin was earlier shown (Riddle and Polhemus) to contain the gonad-stimulating hormone; this now confirmed.

the anterior pituitary. Hitherto, only accelerated body growth was a proved specific response of the growth hormone; and only accelerated gonad growth a proved specific response of the gonad-stimulating hormone.

The recent isolation, identification and assay of a third anterior pituitary hormone by Riddle, Bates and Dykshorn included the demonstration that active milk-secretion in mammals, and the crop-gland response in pigeons are specific responses to this third hormone—prolactin. Some facts essential to that demonstration are here reviewed.

Some data concerning prolan are given. The "luteinizing substance" obtained from pregnant urine probably does not derive from the anterior pituitary. To associate it with the gonad-stimulating principle of the pituitary is considered a serious error.

Commercial antuitrin (Parke, Davis & Co.) is again shown to contain demonstrable amounts of gonad-stimulating (and thyroid-stimulating) hormone.

The enlargement of the liver following the administration of extracts of the anterior pituitary is probably a non-specific, secondary and pathological sequel—illustrating a type of response requiring careful analysis in work with unpurified pituitary extracts. This liver response, like a similarly induced glycosuria, is probably the result of a *functional dysharmony* resulting from the simultaneous presence in the blood—in unusual and non-physiological amounts—of two or more potent anterior principles which never normally thus coexist in the blood.

Hyperplasia of the normally developed thyroid following pituitary administration is a specific response to the gonad-stimulating hormone, or to another anterior pituitary derivative having similar solubilities.

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THE EFFECT OF HORMONES ON CELLULAR PERMEABILITY*

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Hormone action and nervous action (involving the central and the autonomic nervous systems) are the two important mechanisms of bringing about the adjustment of the organism to its surroundings. Excitatory and inhibitory influences are exerted on the various organs of the body resulting in adaptive coördination. The nervous and the hormone mechanism cooperate, as has been shown for example in Cannon's extensive studies.[1] The effects of the discharges of the sympathetic such as occur in rage are enhanced by the liberation of adrenalin. The distribution of the nerves over the whole body and the excitation of large groups of nerves (particularly of the autonomic system) from a small area of the brain make the nervous system an important agency exerting a kind of remote control in the body. In the same way the hormones which circulate in the blood in very minute quantities act to influence various parts of the body in a specific manner. The relationship between nervous and hormone action is known to be still closer since the work of Loewi, Finkleman, Cannon and others (Fryer and Gellhorn [2]) has shown that the stimulation of autonomic nerves leads to the liberation of chemical substances of hormone characteristics. Acetyl choline and adrenalin must be considered as the vagus and sympathetic substances respectively. (As to the significance of acetyl choline as a hormone consult Le Heux.[3])

These facts make it probable that the mechanism of nervous and hormone action may be similar in some respects. Now it has been known for some time that nervous stimulation increases the permeability of the cell (compare Gellhorn,[4] 1929, with bibliography, and Gellhorn and Northup,[5] 1932) and therefore it is assumed that changes in permeability may play an important part in the regulation of cellular activity. This idea is supported by experiments which show that, in general, permeability decreases reversibly in narcosis. For this reason experiments were carried out to determine: (1) whether hormones affect cellular permeability and (2) if permeability changes are specific for different hormones. The latter question seems to be of particular interest from the point of view of the antagonistic action of various hormones.

A recent survey of the literature on this question (Gellhorn [4]) indicated that various observations made on intact organisms were not quite in agreement. Working with the intact organism may lend itself to erroneous

* Paper read before the 17th Annual Clinical Session of the American College of Physicians in Montreal, February 7, 1933. Aided by a grant from the Ella Sachs Plotz Foundation.

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interpretations since uncontrollable changes in circulation may be explained as changes in permeability. Therefore experimental procedures were chosen which permit a more rigid control than do experiments on the intact animal. The first group of experiments was carried out on muscle and skin membranes of the frog.

The muscle membrane made from the abdominal muscles of *Rana temporaria* according to the method of Winterstein [6] and a sac formed from the skin of the frog according to the method of Wertheimer [7] were used. Ringer's solution containing sugar was put on one side of the membrane, on the other was a balanced salt solution. The amount of sugar entering the membrane during different periods of time was determined by the Folin-Wu method. Symmetrical membranes from the same frog were regularly used. In preliminary experiments it was found that the permeability of symmetrical membranes from the same frog was under identical conditions about equal. The differences did not exceed 4 per cent in the muscle experiments nor 9 per cent in those on the skin. The average was 2 per cent in the former and 3 per cent in the latter group, so it was certain that differences greater than 10 per cent caused by the application of the internal secretions or of autonomic poisons must be due to a change in the permeability of the membrane.

The principal experiments made by this method showed that the effect of adrenalin on the permeability of the muscle membrane was dependent upon its concentration. If the dilution was 1 : 1,000,000 the permeability to sugar was increased 21 to 108 per cent. This enormous increase of the permeability was not due to diminution of the irritability, since the internal secretions and the autonomic poisons were always added in such small amounts that no change in the irritability of the membrane occurred. Therefore an increase or decrease in the amount of sugar which entered must have been due to a specific effect on the permeability. Adrenalin in a concentration of 1 : 5,000,000 caused either an increase or a decrease of permeability, while in still lower concentrations (1 : 15,000,000) a diminution of the permeability usually occurred. A concentration of 1 : 50,000,000 was without effect. Corresponding results were obtained on the skin membrane. Here also a regular increase of permeability was found with adrenalin 1 : 1,000,000, while in lower concentrations (1 : 5,000,000 and 1 : 25,000,000) the permeability sometimes increased and sometimes decreased. The sensitivity of the skin was still greater than that of the muscle membrane: even in a concentration of 1 : 50,000,000 adrenalin was observed to cause a decrease of permeability.

Thyroxin caused an increase of the sugar permeability of the muscle membrane in dilutions of 1 : 100,000 and 1 : 1,000,000. An increase in the permeability of the skin membrane was found regularly in concentrations of 1 : 10,000 up to 1 : 1,000,000. In lower concentrations thyroxin was ineffective.

Finally, corresponding experiments were performed with a preparation

of insulin which was free from disinfectants. It was shown that insulin in concentrations of 1/50 unit per cubic centimeter up to 1/200 unit per cubic centimeter regularly increases the permeability of the muscle membrane, and the same effect was obtained on the skin membrane in concentrations of 1/50 and 1/100 unit per cubic centimeter. In still lower concentrations no effect was obtained. In these experiments also, there was no perceptible change in the irritability. The experiments showed that adrenalin, thyroxin and insulin influence the permeability of a surviving membrane when used in about the same concentrations as those in which they exert their characteristic effects on surviving organs under similar conditions.[8] Because of the low concentrations in which adrenalin is found in the body it is to be expected that under physiological conditions adrenalin alone decreases the permeability of the cells, while insulin and thyroxin have just the opposite effect. The observations support the conclusions drawn by Eppinger,[9] Asher and Pfluger,[10] and Wiechmann [11] from experiments on warm blooded animals and man after removal of the thyroid and in diabetes mellitus.

TABLE I

Changes in Permeability of Muscle and Skin Membranes Due to Internal Secretions

	Muscle Membrane		Skin Membrane	
	Dilution	Permeability *	Dilution	Permeability *
Adrenalin	1 : 1,000,000	++	1 : 1,000,000	++
	1 : 5,000,000	+ or —	1 : 5,000,000	+ or —
	1 : 15,000,000	—	1 : 50,000,000	—
Thyroxin	1 : 100,000	++	1 : 10,000	++
	1 : 1,000,000	++	1 : 100,000	++
			1 : 1,000,000	+
Insulin	1/50 and 1/100 unit per c.c.	++	1/50 and 1/100 unit per c.c.	++
	1/200 unit per c.c.	+		

* + indicates increase, and — decrease in permeability for sugar.

Although the results obtained are quite decisive as far as permeability is concerned and also occurred in such low concentrations as to be of physiological significance, it seemed desirable to check and amplify them with a different method in which the physiological state of the preparation was secured by the perfusion method and in which the physiological character of the changes in permeability was proved by its reversibility.

A method devised by Mond [12] was adopted with slight modifications. In a pithed frog the blood vessels supplying the gut, and the gut itself were perfused separately. For perfusion of the capillaries of the gut a cannula was introduced into the celiac artery the gastric branches of which were tied off, preventing perfusion through the stomach and loss of fluid. Through this cannula, by means of a three-way cock, either Ringer's solution or Ringer's solution containing the substance under investigation could be

perfused. The liquid, after passing through the gut capillaries, was collected from an outlet cannula introduced into the portal vein.

The lumen of the gut was perfused with 3.15 per cent glucose solution through a cannula introduced just posterior to the pylorus, the outlet cannula being just anterior to the rectum.

The liquid perfused through the capillaries was divided into samples each of which represented ten minutes of perfusion. These samples were analyzed for sugar by the Folin-Wu method.

Results.[13] Control experiments. In order to be certain that changes in the absorption rate, which was used as the indication of permeability, were due to the administration of the substance under investigation, the perfusion rate was kept constant, the perfusing solutions were well oxygenated, and the first few samples were discarded. The perfusion was started and finished with Ringer's solution and between those periods Ringer plus hormone was used. Complete reversibility of the effects of the hormone added to Ringer's solution was observed in most cases and therefore no difficulties were involved in interpreting these data. In other experiments in which, due to high concentrations of the hormones, irreversible effects were obtained, the interpretation of the results could be based on the general course of sugar absorption obtained in control experiments and others in which hormones in subliminal concentrations had been added. It may be emphasized that although in numerous experiments the sugar absorption remained almost equal over a period of two hours, not infrequently a steady decrease in sugar absorption was observed, although all conditions were kept as constant as possible. This decrease was most marked in the first periods of the experiments. It is very remarkable and indicative of the fact that blood vessels and gut were kept under physiological conditions in this preparation, that in no case was a spontaneous increase in sugar absorption observed in the control experiments. Injury is invariably accompanied by an increase in permeability. (Compare Gellhorn,[4] p. 195).

Adrenalin. In a first group of experiments the effect of adrenalin in concentrations of from 1 : 500,000 to 1 : 25,000,000 was studied. It was found that adrenalin 1 : 500,000 to 1 : 5,000,000 considerably increased sugar absorption (figure 1). It is of interest to note that frequently, as in the curves of figure 1, the effect of adrenalin was greater during the second application. The changes in absorption were completely reversible. In lower concentrations (1 : 10,000,000) a decrease in absorption occurred (figure 2). In still lower concentrations (1 : 25,000,000) the effects were weak. Two characteristic examples were given in figure 3, which show that during the first application a slight decrease in absorption was obtained, whereas in the second perfusion period with adrenalin the sugar absorption was slightly increased. This again seems to indicate that the adrenalin effectiveness is increased during the second period of its application. In our studies not infrequently effects of this type were observed which may be taken as an expression of a cumulative effect upon the cells which allows the sugar to permeate through the gut.

The question arises whether the effects on absorption are dependent upon the changes in the diameter of the blood vessels brought about by adrenalin.

The results of our experiments show conclusively that no relation exists

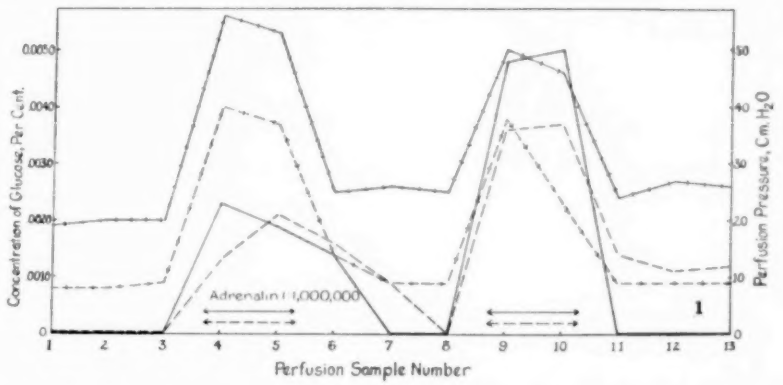

FIG. 1. Experiment A (solid line) and experiment B (broken line) with adrenalin 1:1,000,000, which was administered during the collection of the samples covered by the arrows. Other samples, perfusion with Ringer's solution.

The solid, crossed line shows perfusion pressures for experiment A; the broken, crossed line perfusion pressures for experiment B.

between the vasoconstrictor effect of adrenalin and its influence on sugar absorption. In concentrations of 1:500,000 to 1:1,000,000 the constrictive effect was very marked and accompanied by an increase in absorption. In lower concentrations (compare the curve in figure 2) not the slightest constrictive effect was observed in spite of very considerable changes in

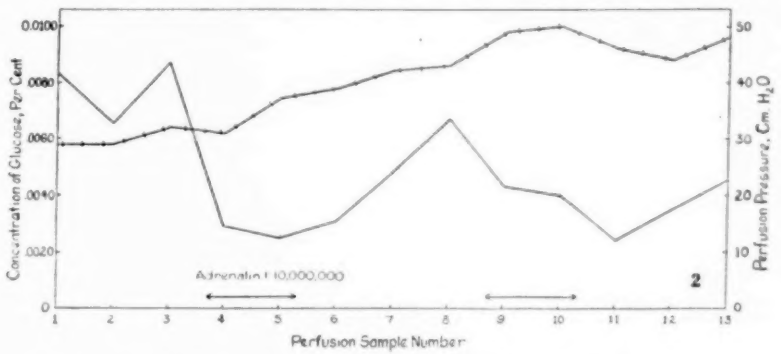

FIG. 2. Experiment with adrenalin 1:10,000,000. Details as in figure 1.

sugar absorption. As was mentioned above, any constrictive effect was at once compensated in order to keep the perfusion rate constant. It may therefore be said that independent of its vascular effects adrenalin displays specific effects on the absorption from the gut which depend on the concentration and consist either of an increase or a decrease in absorption.

Abderhalden and Gellhorn [14] showed in 1923 that in the presence of small amounts of serum the effectiveness of adrenalin upon the heart is greatly increased. The threshold for the positive inotropic action is lowered and the duration of the adrenalin effect is increased. Therefore the question was investigated whether the action which adrenalin has on absorption may also be enhanced by serum. In our experiments frog serum was used

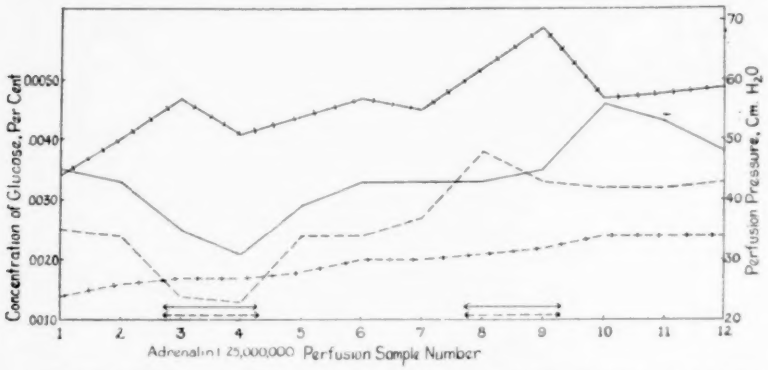

FIG. 3. Experiment A (solid line) and experiment B (broken line) with adrenalin 1 : 25,000,000. Details as in figure 1.

in concentration of 1 : 500 or 1 : 5,000 diluted with Ringer's solution. Control experiments showed that frog's serum 1 : 500 in Ringer alone is without influence on sugar absorption.

Numerous experiments performed with the addition of serum to adrenalin-Ringer in the concentrations mentioned above proved conclusively that adrenalin in such solutions is more effective in influencing sugar absorption than in pure Ringer's solution. In the presence of serum, adrenalin was effective even in a concentration of 1 : 50,000,000 and increased sugar

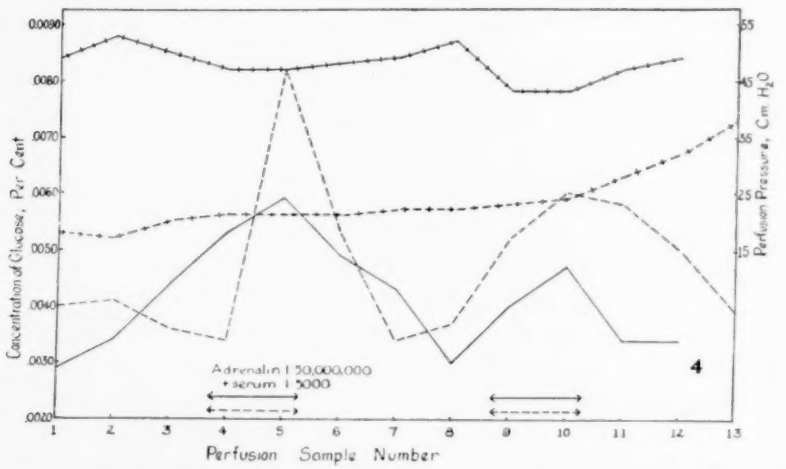

FIG. 4. Experiment A (solid line) and experiment B (broken line) with adrenalin 1 : 50,000,000 plus serum 1 : 5,000. Details as in figure 1.

absorption reversibly. Such action in the absence of serum requires a concentration of adrenalin of at least 1 : 5,000,000. These marked effects of adrenalin on absorption were not accompanied by vasoconstriction, as is shown in figure 4.

Thyroxin. The experiments with thyroxin were carried out in concentrations of from 1 : 50,000 to 1 : 200,000. The pH of Ringer's solution with and without thyroxin was adjusted to the same value (pH = 7.6). The effect in concentrations of 1 : 50,000 was regularly a marked increase in the absorption of sugar which frequently was more or less irreversible, as shown in experiment A in figure 5. This interpretation is justified,

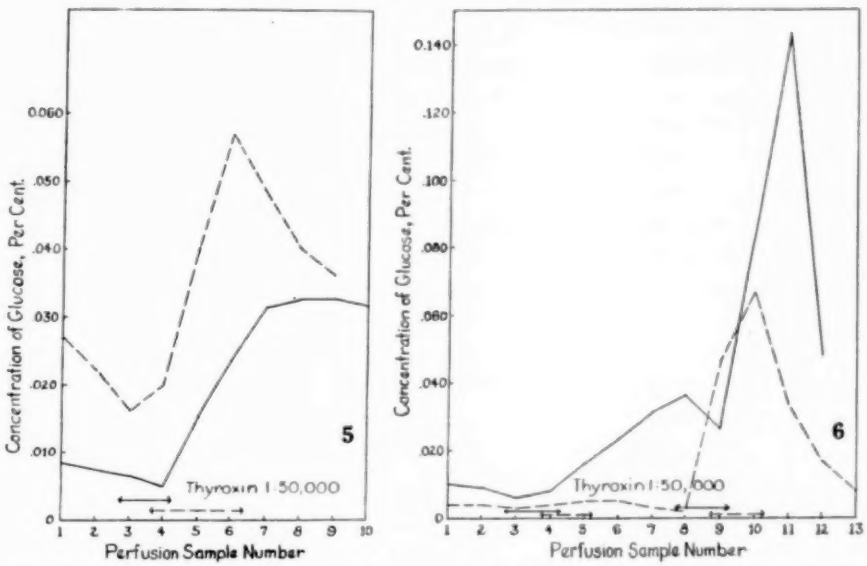

FIG. 5. Two experiments, A (solid line) and B (broken line), with thyroxin 1 : 50,000.
FIG. 6. Two experiments, A (solid line) and B (broken line), with thyroxin 1 : 50,000. Graphs of perfusion pressures not given; otherwise details are as in figure 1.

since, as was already emphasized, a spontaneous increase in sugar absorption never occurred. Occasionally this increase was delayed, as experiment A in figure 5 indicates. As was shown in the work with adrenalin, an increase in sensitivity to the same drug during its second application was also observed with thyroxin, but to a much greater extent. In fact, it was this group of experiments which called our attention to this phenomenon. Figure 6 gives an example. In both cases the thyroxin effect is very marked during the second application, while it is either completely or almost absent during the first. One also obtains the impression from these experiments that the speed with which the reaction is brought about is greater during the second than during the first application of the drug. That is particularly distinct in experiment A, in which the increase in sugar absorption occurred with very great delay during the first part of the experiment but

much faster in the second period, although even here after the perfusion with thyroxin.

It is significant that thyroxin never influenced the perfusion rate. In the concentrations mentioned above it was without influence on the capillaries, causing neither contraction nor dilatation.

In concentrations of 1 : 100,000 an increase in sugar absorption was also observed. In this concentration there was again a characteristic increase in sensitivity in the second application of thyroxin. Frequently the first application was without effect, while the second caused a marked increase in sugar absorption. This increase was characteristically delayed, occurring after the perfusion with thyroxin was over.

Only a slight increase in sugar absorption occurred in experiments with thyroxin 1 : 200,000. Still lower concentrations were not examined.

Another series of thyroxin experiments was performed in the presence a serum (frog's serum 1 : 500 in Ringer's solution). Neither the type nor the range of concentrations in which thyroxin was effective was changed.

Insulin. A preparation from Lilly (Iletin) was used. Since it contains 0.2 per cent phenol, corresponding amounts of phenol were added to Ringer's solution so that it differed from insulin-Ringer only by its insulin content. Insulin was examined in concentrations of from 0.02 to 0.0033

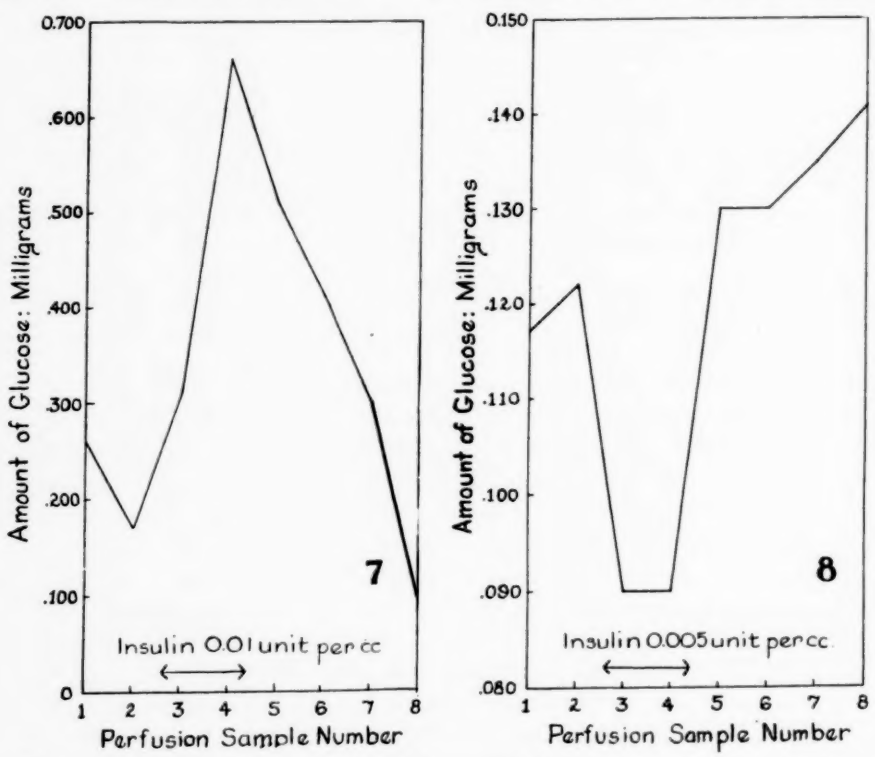

FIG. 7. Experiment with insulin, 0.01 unit per cubic centimeter. Details as in figure 5.
FIG. 8. Experiment with insulin, 0.005 unit per cubic centimeter. Details as in figure 5.

units per cubic centimeter. Figure 7 shows that insulin in a concentration of 0.01 unit per cubic centimeter increases absorption. With 0.02 unit per cubic centimeter the effect is the same, but it is frequently irreversible. Occasionally a delayed effect was observed: i.e., the greatest increase in sugar absorption occurred in the Ringer periods which followed the application of insulin. Five-thousandths unit per cubic centimeter decreased reversibly the absorption of sugar, as shown in figure 8, but 0.0033 unit per cubic centimeter was without any effect. In these experiments the question was also investigated whether the addition of small amounts of serum as used in the previously described experiments had any influence on the insulin effect. The result was a distinct decrease in the insulin effect in the presence of serum.

As in the thyroxin experiment, the perfusion rate remained unchanged in the insulin periods. Therefore the insulin influence on sugar absorption cannot depend on vascular effects.

Hormones of the Hypophysis. A great many experiments were performed with the hormones of the hypophysis. We used pituitrin (Parke Davis and Company) and powderized dried gland of the posterior hypophysis in concentrations ranging from 1 to 40 units per liter. There was no effect on the permeability of the gut to glucose, the concentration of the latter remaining either unchanged in the blood vessels or showing a slight gradual decrease as was observed in control experiments without the addition of a hormone. But it seems worth while mentioning that the hormone has a distinct effect on the blood vessels supplying the gut. They showed a marked constriction while the hormone of the posterior hypophysis was flowing through the blood vessels and this is indicated in figure 9, by the rise in pressure which was necessary to maintain the same output. The effect is quite

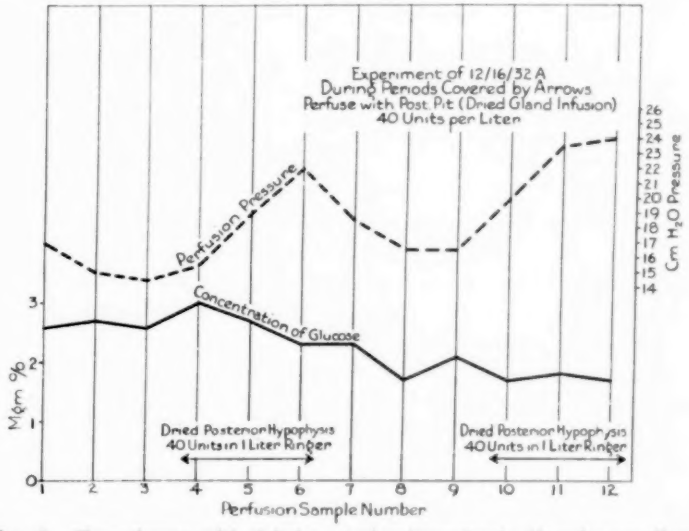

FIG. 9. Experiment with dried posterior hypophysis 40 units per liter.

reversible. These experiments emphasize again that there is no relationship between the effects of a substance on blood vessels and on permeability. Thyroxin and insulin showed profound effects on permeability without influencing the blood vessels at all; the adrenalin effects on permeability were not in proportion to the degree of vasoconstriction and the observations with posterior hypophysis show vasoconstriction without permeability changes.

Since in absorption experiments on intact animals a distinct retardation in absorption was observed by Thienes and Hockett[15] after administration of extracts of the posterior hypophysis it must be concluded that this change in absorption is not due to an alteration in permeability but simply to a vascular effect. Just this example may be a good illustration of how necessary it is to control rigidly the circulatory conditions if an analysis of a drug or hormone effect in regard to permeability is desired.

A careful study of the effects of antuitrin (Parke, Davis and Company) on absorption of sugar in concentrations of from 1 : 125 to 1 : 1000 was completely negative. Referred to the concentrations of fresh anterior lobe of the hypophysis the concentrations are 0.96 per cent to 0.12 per cent. There were also no effects either on the blood vessels or on the gut.

Acetyl Choline. The experiments with acetyl choline were carried out under the same conditions, and concentrations varying between 1 : 50,000 and 1 : 40,000,000 were used. The results are very striking and are essentially different in high and low concentrations. In the first case (figure 10)

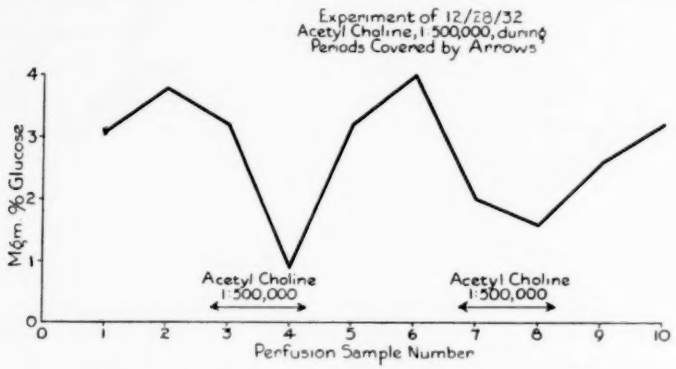

FIG. 10. Experiment with acetyl choline 1 : 500,000.

a decrease in sugar absorption invariably occurs, whereas in low concentrations the absorption of glucose increases. The latter effect is weaker than the first. Both effects are reversible.

These experiments are particularly interesting in comparison with the results obtained with adrenalin. The antagonism between the sympathetic hormone adrenalin and the parasympathetic hormone acetyl choline is quite evident. Low concentrations of adrenalin, such as may be of physiological significance, decrease permeability, whereas acetyl choline increases it. In high concentrations the same antagonism obtains since adrenalin increases

permeability, whereas acetyl choline lowers it. The frequently stated antagonism between the sympathetic and parasympathetic nervous systems which also can be demonstrated, as is well known, by the study of drugs which stimulate the sympathetic and vagus respectively, holds true as our experiments prove in reference to permeability (Gellhorn and Northup [16]).

Discussion. The experiments described in this paper show conclusively that hormones influence permeability in a specific manner. The effects are practically identical in muscle and skin membranes, and in the gut wall. They occur in concentrations similar to those in which these substances produce well known effects on heart, blood vessels, metabolism, etc. It may therefore be said that the permeability effects described in this paper are equally significant from a physiological point of view. That is to say, the results are not simply of pharmacological interest.

Concerning the influence of hormones on absorption, ample experimental evidence is given that the effects are independent of changes in the diameter of the blood vessels. It is not quite clear as yet whether or not changes in permeability of capillaries are at least partially responsible for the changes in absorption which were obtained under the influence of different hormones. But it may be said that substances which affect the bore of capillaries and arterioles markedly do not necessarily change their permeability provided that the alteration in circulation is compensated by appropriate changes in perfusion pressure.

Summary. Experiments on muscle and skin membranes and on the gut were carried out in order to determine the influence of hormones on permeability under well controlled conditions. It was found that adrenalin, thyroxin, and insulin increase permeability in relatively high concentrations; a decrease in permeability was caused by low concentrations of adrenalin and insulin. Small concentrations of serum increase the effect of adrenalin and diminish that of insulin.

Acetyl choline behaves as an antagonist of adrenalin in regard to permeability.

The hypophysis hormones are without effect on permeability.

The permeability effects of hormones are independent of changes in the diameter of capillaries and arterioles which they may produce.

The physiological character of the experiments is evident (1) from the reversibility of the permeability changes, and (2) from the fact that the changes in permeability occur in concentrations similar to those which affect heart, blood vessels, and metabolism.

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UNDERNUTRITION AND ITS TREATMENT BY ADEQUATE DIET*

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The definition of the state of undernutrition is of necessity somewhat arbitrary. Although occasional reference is seen to absolute weight deficiencies, the usual practice is to consider the weight deficit with reference to other personal statistics. The theoretically ideal weight for a given age, sex, and height may be obtained from many statistical studies.[56] A deviation of over 10 to 15 per cent below an ideal weight may be regarded as undernutrition.[15, 48] In our series we have arbitrarily set 15 per cent as the critical level. We have not attempted the intricate differential diagnosis between undernutrition and simple underweight.[5]

The condition may be acute or chronic. In acute undernutrition it is usually conceded that the weight loss has a direct relation to a period of inadequate food intake. Chronic undernutrition on the other hand is regarded as a new type of phenomenon for which an explanation must be sought. The hypotheses which have been advanced in the literature may be grouped into those which postulate (1) anomalies of metabolism, (2) unusual conditions of the endocrine glands or (3) peculiarities of the nervous system, especially the basal centers. A careful review of the available literature fails, in our opinion, to support adequately any of these proposed explanations. In contrast to these conceptions, the principle may be expressed that chronic undernutrition, like acute undernutrition, is always the result of a dietary inadequacy. The reasons why the diet is inadequate may vary in chronic states just as they do in acute conditions. On the basis of this assumption a number of patients suffering from undernutrition both of the acute and chronic forms have been treated by dietary measures. The present report summarizes our experience with this method of treatment over a period of four years.

Factors Producing Undernutrition

In the present consideration of undernutrition, the attention is focused upon the non-specific forms. It is recognized that certain accessory food substances are required to prevent scurvy, pellagra, beri-beri, etc. These fully developed conditions due to vitamin deficiency are relatively rare in our modern conditions of life, although some of the less dramatic forms of undernutrition may possibly be associated with relatively low vitamin intakes.[25, 45, 60]

The dietary protein is again a matter of great importance. The qualita-

* Received for publication November 11, 1932. From the Medical Service of the Western Pennsylvania Hospital.

tive variations in the common food proteins have been long recognized.[32, 45] In practice the purely quantitative aspects are perhaps of more immediate importance.[47] The serious effects of prolonged lack of protein intake have been reviewed by Lusk.[33] In certain types of undernutrition low plasma proteins [46] and edema [52, 65] are probably associated with subminimal protein intake. It is also important to recognize that the minimum protein intake is not necessarily the optimum protein intake.[9, 41, 53, 58]

The importance of heredity as an etiologic factor in undernutrition has been subject to considerable discussion. Some authors regard leanness as a deeply seated constitutional tendency which is quite unaffected by increased feeding.[37, 66] There exists, however, a belief that although undoubtedly heredity influences certain special characteristics of the individual, the nutritional state is more directly the result of his environment. Hereditary phenomena may perhaps be considered as relatively more conspicuous in infants and young children. Hence the increased significance of the statement by Holt,[15] "The second group, in which malnutrition is an acquired condition, is the larger one. The principal causes are ignorance or neglect of the common rules of hygiene, the observance of which is essential to normal healthy growth." In dealing with adults the point may be made that what is often considered hereditary influence is in reality the result of environment in the form of a family custom of inadequate feeding which becomes fixed in childhood and persists as faulty eating habits through adolescence to maturity.

Endogenous thinness or undernutrition due to an endocrine disorder is a conception which has a popular appeal. Many authors are somewhat vague as to the exact significance of the term, endogenous undernutrition. By definition and as specifically stated by certain writers, this condition means a thin state which results from a dysfunction of one or more endocrine glands. The implication necessarily exists, and in some papers the statement is made, that this effect is produced by an endocrine imbalance regardless of food supply. From this point of view undernutrition has been described as the resultant of an imbalance of the endocrine glands as a group or as the resultant of defects of certain specific glands.[23, 30, 31, 50, 63] In practice the identification of these specific types of undernutrition on the basis of either metabolic or anthropometric evidence [23, 63] would be a matter of considerable difficulty.

It is perhaps only natural that leanness should be attributed to abnormal function of the thyroid gland. Although a loss of weight frequently parallels an abnormally high level of metabolism, undernutrition as part of a hyperthyroid state is not included by most authors in the category of endocrine undernutrition. A variety of endocrine undernutrition which is associated with a hypothyroid state has been reported. A characteristic fat distribution for this state has been described [63] although most authors appear to have made the diagnosis on the basis of the metabolic data.[64] A low basal metabolism is generally recognized as present in chronic thin states.[10, 42]

It may definitely be questioned, however, whether this low metabolism is a result of hypofunction of the thyroid gland.[22, 44] Thyroid extract has been given to many undernourished patients to elevate the metabolic level.[3, 44, 64] The clinical response did not parallel the increase of metabolism[3, 64] although a number of patients experienced a definite increase in appetite.

The relation of undernutrition to dysfunction of the pituitary gland has been enthusiastically advocated. Here again the identification of the clinical type from either the anthropometric[63] or the metabolic data[16] is difficult. Frequent reference is seen to Simmonds' hypophyseal cachexia[6, 19, 50, 51, 66] as a severe form of emaciation resulting from hypophyseal disease. The advanced condition is rare, but it has been suggested that milder forms of pituitary leanness may be more common.[66] There is, however, considerable reason to question the etiologic relationship between hypophyseal disease and severe undernutrition.[3, 19]

The possibility that a functional insufficiency of the pancreas, especially of the islands of Langerhans, may act as a cause of undernutrition has been suggested.[13] This conception has resulted in an extensive literature relative to the use of insulin in the treatment of chronic thin states. These reports appear to agree regarding the beneficial results of insulin therapy. There are, however, two distinct schools of opinion as to the mechanism whereby this improvement is brought about. One group of investigators feels that insulin promotes a readjustment of certain factors of the cell metabolism whereby a gain in weight is permitted. The second school attributes the weight gain and the clinical improvement to the increase in food intake which results from the improvement in appetite due to the use of insulin. The views of the first group are summarized in the discussion of Metz.[38] The report of Short[57] is perhaps typical of those who feel that the principal influence of insulin is upon the appetite. He emphasized the fact that when patients can be induced to eat, the improvement is rapid. In addition to the animal experimentation of Macleod[35] a number of careful clinical studies have been reported.[1, 4] This evidence appears to indicate that insulin greatly stimulates the appetite, thus promoting the ingestion of large quantities of food and thereby the increase of weight.

The coexistence of endocrine disorders and undernutrition may not be doubted. In reviewing the conceptions regarding the relation of the endocrine glands, individually or as a whole, to undernutrition three points must be kept in mind: (1) the criteria which are used as indices of endocrine gland malfunction, (2) the possibility that an observed abnormality of endocrine gland function might be the result of the undernutrition and (3) the probability that the relation of specific endocrine disease to an existing undernutrition is concomitant rather than causal.

The diagnosis of specific endocrine types of undernutrition is impeded by the paucity throughout the literature of descriptions which permit the identification of the several specific types. Those criteria which exist[16, 63] are somewhat difficult of practical application. The use of the basal meta-

bolic level as an index of thyroid function alone has repeatedly been questioned.[24, 44] Furthermore, alterations of the specific dynamic action of food[36] are not reliable diagnostic aids in endocrine disorders[34] and specifically not so in disorders of the pituitary gland.[23, 34, 40, 61]

The evidence that endocrine disorders may result from undernutrition is abundant.[2, 18, 33, 50] The studies of starvation which have been reviewed at length by Lusk[33] afford many illustrations. Chronic undernutrition frequently results in amenorrhea in the female.[33] The effect on the male has been indirectly shown by loss of libido and sexual power.[39] The anatomic changes in certain endocrine glands as a result of undernutrition have been described in great detail.[17, 28, 29, 59] The effect of the war upon the incidence of endocrine disease[12] has repeatedly been mentioned. Perhaps the most spectacular evidence is cited in the work of Stefko[59] who described his observations in Russia. His conclusion that underfeeding causes endocrine disturbance is quite convincing. From another point of view it may be urged that normal cell function is dependent upon an adequate food supply. The effect of lack of iodine on thyroid function is well known. The close chemical relationship of certain hormones to specific amino acids and the possibility of their derivation from these acids[12] emphasize the importance of the supply of food proteins.

When proved endocrine disease is found in association with incipient or fully developed undernutrition, it does not necessarily follow that the undernutrition is a direct consequence of the glandular disorder. The undernutrition is rather the result of the failure of the food intake to approximate the daily energy requirements. Perhaps the clearest illustration of this fact is provided by the work of Shelling[55] on parathyroidectomized rats. It was definitely shown that the test animals became emaciated as a result of a failure to eat and regained the lost weight promptly when the food intake was resumed. The reason why the animals would not eat certain foods appeared to be related to the glandular dysfunction. However, if a diet qualitatively proper was provided, the undernutrition disappeared. Clinically this identical phenomenon has been observed in thyroid disease and in pituitary disease. The disease may continue unrelieved but the nutritional state may be altered by proper feeding. This point will be further elaborated in the discussion of energy balance.

Closely related to the conceptions relative to the endocrine regulation of undernutrition are those which postulate a disturbance in function of the central nervous system as the etiologic factor. The most common opinion states that centers exist in the mid-brain which specifically regulate metabolism regardless of food intake.[19, 66] The intervention of the sympathetic nervous system in the metabolism of food has also been described.[11, 27]

Again, as in the case of the endocrine apparatus, there is no question as to the coexistence of disorders of the nervous system and of undernutrition. The contrasting point of view states that the abnormalities of the nervous system are frequently secondary rather than primary. The development of

instability of personality has been repeatedly described in starvation [32, 33] and the lesser degrees of undernutrition.[2] The effect of undernutrition on the sympathetic nervous system and particularly the functioning of the vagus nerve has been reviewed by Levine.[28] Severe forms of nervous disorder are more frequently identified with the specific undernutrition associated with avitaminosis.[14] The dementia of pellagra is well known as are the lesions of the nervous system due to the absence of vitamin B. The cord degeneration of pernicious anemia may also be mentioned. In the very serious form of undernutrition, "anorexia nervosa," the close relationship of undernutrition and central nervous system function is well recognized.[3, 44, 50] When this advanced stage is reached, it is not always easy to determine causality.

The importance of the energy balance as a factor in the development of undernutrition has been much debated. After the discovery of vitamins there was a tendency to minimize the energy factors. The increase in knowledge regarding the autonomic nervous system has also shown new potential regulatory mechanisms. Certain discussions of these phenomena convey the impression that these factors are of primary importance.[7, 30, 66] There is no doubt that the endocrine glands, the accessory food substances, and the autonomic nervous system may influence the intermediate metabolism of many specific types of food. There is also no doubt that these influences cannot initiate the supply of necessary material. It is, moreover, a fair criticism of certain of the published case histories of alleged endocrine or medullary undernutrition that the patients were not adequately fed during the periods of observation.

Caloric intake is determinable with relative ease and a few observations have been made of the relation of food intake alone to weight changes.[20, 43]

The absence of a reliable method of clinical application for the determination of total caloric output is one of the chief obstacles to the absolute proof of the preëminence of energy balance in nutritional states. Apart from observations of basal metabolism and specific dynamic action, the caloric output can rarely be approximated. The variations in energy expenditure that occur during periods of work, and of work-free time, and the great variability of personal habits make an estimation of output under normal conditions quite unreliable.[21, 26, 54] The endocrine or hereditary etiologies of leanness postulate undefined abnormalities of energy output.[37] High energy outputs are readily recognized in thyrotoxicosis and fever, the two conditions in which rapid and spectacular weight changes are obviously attributable to energy deficiency. In the more chronic forms of undernutrition, numerous investigations have failed to reveal any abnormal increase in output. The existence of an abnormality of specific dynamic action in association with undernutrition [36] has been questioned [23, 61] and the etiologic importance of a possible small variation in this factor may be regarded as very slight.[10, 47, 61] The basal metabolism is uniformly reported as normal or low. Furthermore, the reduction in the body mass which must be trans-

ported, and the inactivity due to semi-invalidism further reduce energy output. The total energy output in chronic undernutrition is, therefore, much diminished as compared with health.

In discussions of energy relations emphasis must not be placed upon the intake or the output of energy but upon the energy balance. Except in conditions of constant true weight balance, the caloric intake in no way reflects the caloric output.[49] Given a negative caloric balance, the weight loss is determined by two factors: (1) the magnitude of the negative balance, which defines the rate of change and (2) time, which defines the total change. It is general experience that acute illness is almost uniformly accompanied by a fickle appetite and consequent low food intake. The combination of lowered intake and elevated output exaggerates the energy deficit and produces an appreciable rate of weight loss. In more protracted illness, with the exception of a few conditions like thyrotoxicosis, the same fickle appetite prevails. Here, however, the output of energy is much diminished. The negative energy balance is due almost entirely to the diminished intake.[23] The rate of weight loss is small. The time factor then becomes of great importance in the determination of the total weight loss.

However, in neither acute illness nor in chronic illness is a weight loss an inevitable consequence of the disease. In acute febrile states no weight loss occurs if the food intake is forced up to cover the excessive output as was first demonstrated by Coleman and DuBois [8] in typhoid fever. Likewise, in thyrotoxicosis, no weight loss develops if the intake is adequate (patient 18 and other unpublished cases of our series). In the more protracted illnesses, weight loss may be checked or weight may be gained by forcing up the energy intake as Berkman [3] and others [1, 44] have done in advanced cases of anorexia nervosa and Riecker and Curtis [51] in the marked undernutrition associated with Simmonds' disease. These results have been further emphasized by Shelling [55] in his work on experimentally produced cachexia parathyreopriva.

Thus there appears to be no more fundamental difference between the acute and chronic types of process than that of rate of development. The frequently mentioned "exogenous" undernutrition may perhaps be called "acute" undernutrition whereas the "endogenous" may be called chronic undernutrition. The characteristic which is common to people who have lost large amounts of weight is that they have lived long enough after the onset of disease, be it mental such as dementia praecox, neoplastic such as cancer of the stomach or adenoma of the pituitary gland, or infectious such as tuberculosis or an intractable pyelitis, to have suffered a significant total weight loss. The development of secondary disturbances of the several endocrine glands, of the nervous system, or of other corporeal systems as a result of the prolonged undernutrition often obscures the primary etiologic factor in the clinical picture which it presents. When, as frequently occurs, the background for chronic undernutrition is laid during the growth period

of childhood or adolescence, certain anatomical changes are to be expected in all organs including the endocrine glands. When the period of underfeeding begins after maturity, both the anatomic and physiologic abnormalities resulting therefrom may be less conspicuous.

Principles of Treatment

The basic principle which was followed in the treatment of these patients is that, given a general mixed diet with no specific food deficiencies, the intake must exceed the output in order to produce a gain in weight. The rate of gain in weight is determined by the amount by which the intake exceeds the output. The total gain in weight is determined by the rate of gain and by the duration of the period of treatment.

The amount of food which ordinarily must be ingested in each twenty-four hour period in order to secure a reasonable rate of weight gain was found to be 3000 to 3500 calories. The criteria which have been advocated for the estimation of the desired intake from the kilograms of body weight appeared to us to be unnecessary. If they are employed, 65 to 75, or even 90 calories, per kilogram of actual weight should be given. On the basis of ideal weight, these values become proportionately less. The exact level of intake is determined primarily by the rate of weight gain desired. Not all patients were able to ingest the full diet at once. In special cases, we have used diets of 2200 to 2500 calories for three to four days. In practically all cases it was a simple matter to step up the intake to 3500 calories after a week or two on a 3000 calorie diet. A 3500 calorie diet produced an adequate rate of gain in the ordinary case. Higher levels have been used on special cases, the maximum for our series being 5100 to 5300 calories.

The distribution of these relatively large food quantities into meals is of considerable importance. In the hospital series, the total daily intake was divided into approximately equal calorie meals. Intermediate feedings were the rule in the office patients and were generally successful. Great stress was laid upon regularity in eating habits in connection with the training of the gastrointestinal tract to its new duties. A large number of the patients habitually had eaten one or, at most, two adequate meals per day. In most cases breakfast was the meal which was slighted or omitted. The reëducation of patients in this single respect is a long step toward improvement. In order to permit the stomach to empty before the noon meal, breakfast must be eaten early in the morning. In the hospital the meals were served at 7:30, 11:30 and 4:30. In the office practice, we encouraged our patients to get up early enough so that they could eat a proper breakfast.

The type of food which was employed in these diets was considered as of less importance than the caloric value. There were, however, certain factors which required specific attention. The protein intake was usually set at one gram per kilogram of ideal weight, which corresponded to 50 to 70 grams. On the basis of actual weight the proportion varied between

1.3 to 1.5 grams per kilogram. As will be shown later in the studies of nitrogen balance, this supply of protein covered the daily need with ample residue for storage. Occasionally the protein intake was raised to 90 to 100 grams when a peculiar reason appeared to exist. These higher levels usually accompanied the very high intakes such as 4500 to 5000 calories. The adequacy of the protein, that is, its biological value, was secured by the liberal use of beef, milk, eggs and similar substances of animal origin although a fair amount (30 to 40 per cent of the protein) was often given in the less complete vegetable proteins. Due care was also taken to insure an adequate supply of the vitamins and salts. The liberal use of fresh vegetables, butter, milk and eggs undoubtedly more than covered the daily need. Cod-liver oil, viosterol, yeast, wheat germ preparations and other concentrated vitamin preparations have been used at times without perceptible influence on the general course of events.

Our series showed that patients will gain weight on high fat diets or on high carbohydrate diets. Diets with fatty-acid-glucose ratios varying from .5 to 3.2 have been used and adequately handled by the body. The problem of potential acidosis with the higher ratios has not appeared to be important in our series. The advantage of the high fat diets was the small bulk; the disadvantages were the high satiety value and the prolonged stomach emptying time. High fat diets were harder to follow for any prolonged period of time. The high carbohydrate diets were distinctly more palatable and contained the types of food to which the average patient is accustomed. The large volume occupied by these foods was a handicap to many patients. However, in addition to the greater palatability of these lower energy foods, there is perhaps a definite advantage to be derived by the systematic mechanical distension of the stomach and intestines which is secured by diets of moderate bulk.

Since the present thesis requires a positive energy balance for the gain of weight, we must consider also the output of energy. The basal metabolism in the majority of patients was low, although not abnormally low for the actual mass of the patient. The extrabasal energy output may be divided into the heat of specific dynamic action, the work energy and the non-work fraction. It is obvious that since the specific dynamic action varies with the food intake, an increase in output from this source is inseparable from an increase in energy intake. This extra heat loss, however, does *not* approximate quantitatively the extra energy taken in. The work fraction in most cases may be sharply reduced. Often 500 to 1000 calories a day may be saved. The energy loss from other sources, not work, is very hard to estimate because of the difficulty in analysis of individual habits. In two respects great savings in energy output of this nature may be secured. During 12 to 14 hours a day this factor may be minimized by requiring absolute rest in bed. In addition to the nine or more hours rest each night, rest periods were required for an hour after each meal. The importance of post-prandial rest periods cannot be over-

emphasized and we consider them one of the most valuable items of the regime. They are of benefit not only in that they increase the total daily rest from 20 to 30 per cent but also they are of particular value in promoting rest at times when the physiological reserves of the body, especially of the circulatory organs, are subject to the increased strains consequent upon food handling. The second economy may be effected by a reduction of the purely waste energy resulting from the thousands of purposeless movements which are so commonly noted in thin subjects. Liberal doses of bromides were of great assistance in reducing muscle tension, fidgeting, and purposeless movements.

In summary we may review the most important factors in the energy balance. The energy intake may be raised to 3000 to 3500 calories. This often means an increase of 1000 to 1500 calories over previous levels. With reference to energy output, no economies can be expected in either the basal fraction or the specific dynamic action fraction. In fact both factors tend to increase somewhat. The greatest single potential energy saving lies in the elimination of 500 to 1000 calories of the work fraction. The portion of the non-work, extra-basal energy which may be spared cannot be determined but perhaps may reach a few hundred calories. From these approximations, it may be seen how it is possible to create a positive energy balance of sufficient proportions to permit a reasonable rate of weight gain.

From the practical standpoint, there are certain important economic aspects to dietary procedures. Two of the chief factors in this respect are (1) cost of food and (2) the economic status which permits adherence to the specific routine. Contrary to expectation, high caloric diets are not necessarily inordinately expensive. It was found that the total cost of the various foods which form the back-bone of high caloric menus, such as meat, cream, butter, and bread, was, in the amounts eaten, much less than that of the fruits and vegetables in the same diet. The second economic factor consists of the requirement that the patient be able to adhere to the specific routine which is demanded. It is our practice to insist that nothing in the patient's routine must interfere with the schedule. It is, in our opinion, impossible properly to treat a serious case of undernutrition while the patient continues at work.

In undernutrition, psychic influences are of considerable importance especially because of their effects upon appetite. Two important factors of this type center around the environment and the food supply. An environment which produces frequent emotional crises is incompatible with successful treatment. These environmental difficulties often take the form of over-solicitous parents or relatives. One of the most significant advantages of institutional treatment lies in the endless routine cycle of food, rest, and visits. In non-institutional patients a similar "low-grade" daily routine can be devised. It is in regard to the food itself that the worst psychic handicaps are usually encountered. Many undernourished patients

have long lists of specific food repulsions. After reasonable coöperation on the part of the cook or dietician is ensured, due recognition must be taken of the important rôle which bad eating habits have played in the development of the existing status. A reëducation of the patient's likes and dislikes is almost always indicated and is essential to the permanence of any weight gains which may be secured.

In addition to an adequate regime and the ability to follow the regime, a third requirement for success in the treatment of undernutrition is a genuine desire on the part of the patient to improve his condition and a capacity for self discipline. The reëducation of the habits of many years requires a certain strength of character even under the most favorable conditions. If a desire for a gain in weight is a whim of the moment or if the program is reluctantly accepted under pressure, a weight gain will be secured only insofar as, and only for as long as the patient persists. Significant changes in body weight cannot be produced in a few days. Success, therefore, depends upon the will of the patient to carry on.

Methods of Observation

The present study is based upon the observations made upon 41 patients during a period of four years. Twenty patients were studied on the metabolic pavilion of the hospital and 21 were office patients. Two patients of the hospital series were classed as failures in spite of known control. The data of these cases will be analyzed separately.

The weight records of private patients treated in the office were single observations of body weight without clothes which were taken on a good office scale at weekly or longer intervals. The weight records of the hospital patients were the average of three daily determinations taken under basal conditions on a special scale. In the estimation of probable true weight changes, it was felt that the averages of the weights observed on the day before, the day of, and the day after the beginning and end of a period of observation gave figures in which the influence of the normal daily fluctuation in residual water was minimized. In patients whose dietary treatment started on the first day, the average of only two days was taken. Likewise a few patients did not remain in the hospital beyond the period of observation and, therefore, lacked a weight record for the day following the cessation of treatment.

The food intake in the case of most of the office patients was not weighed. A few were required to purchase food scales and were provided with weighed diets. There was, therefore, no record of the exact intake of this group. All hospital patients were placed on a rigid metabolic regime. The observations of intake of this group were, therefore, of a high degree of accuracy.

Observations

Initial Status of Patients. Of the 39 patients successfully treated, there were 31 women and 8 men. This proportion, in our opinion, in no way in-

dicates the relative predominance of undernutrition among women. The ages of the patients varied from 10 to 35 years in the hospital series and from 22 to 61 years in the office series. The average ages were 26 and 37 years respectively. It will be noted that with one exception, children were excluded from this study.

In stature the subjects varied quite as markedly as in age. In the hospital series, the height varied from 51.7 inches to 68 inches with an average of 63.5 inches. In the office series the variation was from 59 to 72.5 inches with an average of 65.5 inches.

The initial weights of the entire group averaged 46.9 kilograms. In the hospital series the weights varied from 21.2 kilograms to 54.1 kilograms with an average of 42.5 kilograms while in the office series they ranged from 35.4 kilograms to 63.1 kilograms with an average of 50.7 kilograms. For the purposes of this study, the relative weights are of greater significance than the absolute weights. The probable ideal weights of the individuals appear in column 5, tables 1 and 2. From the data in column 7, it will be seen that our subjects averaged 24 per cent below their ideal weights. In the hospital series they ranged from 13 per cent to 42 per cent with an average of 26 per cent while in the office series they averaged 22 per cent varying from 11 per cent to 39 per cent. Four patients, one in the hospital series and three in the office series, were not sufficiently below ideal weight to be classed as cases of undernutrition according to our defined standard. The hospital case, number 16, was a readmission for a second and postoperative period of metabolic study of patient number 15. This case will be discussed below. The three office patients presented clinical pictures similar to those of the rest of the series. They were included in order to emphasize the point that the degree of undernutrition does not necessarily influence the response to treatment. In the hospital series, patients 13 and 16 were repeat periods on patients 12 and 15 respectively. In each case the first period was preparatory to operation and the second period postoperative after a lapse of the several weeks immediately following the operation in order to permit metabolic stabilization. In the office series, patient Q was a repeat period three years after the first treatment (P) during which the patient dissipated much of her previous gain. T and V were also repeat periods on patient S at intervals of two and four years respectively. These repetitions will be discussed in more detail below.

The clinical pictures which were presented by these patients were greatly varied. In one patient, number 6 of the hospital series, the malnutrition might be described as *acute*. This patient was recovering from pneumonia followed by empyema. Patient 18 represented an acute exacerbation due to thyrotoxicosis of a chronic malnutrition. Patient O of the office series had an acute malnutrition produced by a misguided diet. The remaining patients of both series could be classed as chronic types. In some the condition had existed since childhood. These cases fell into the so-called "hereditary" groups. The other patients had been underweight for many

years although in some cases a recent acceleration of the weight loss was responsible for consultation with the physician.

The symptoms which were presented by our patients covered almost every system of the body. Palpitation, tachycardia, precordial pain, dyspnea, dizzy spells, especially on sudden changes of position or on prolonged exertion, were frequently mentioned. Many patients had discovered a limitation of their endurance. Some patients complained of irritability, nervous tension, inability to relax, insomnia. Others described weakness, lack of ambition and even lethargy as important symptoms. The majority of patients could be definitely regarded as unstable personalities.

The frequency of occurrence of specific endocrine disorders will vary with the conceptions of the observer as to what evidence indicates disorder of a given gland. In this series we have encountered frank thyrotoxicosis. Dysmenorrhea was frequent among women. Metrorrhagia and amenorrhea were noted, although in many other instances the menstruation was perfectly normal. Phenomena which are sometimes attributed to malfunction of the suprarenal glands such as instability of the circulatory apparatus, dizzy spells, low blood pressure, wide pupils, were often noted but were by no means constant. Headaches were frequent and often severe but no patient presented symptoms of intracranial pressure or other clear cut pituitary characteristics.

In many of our patients, especially of the hospital series, specific types of disease were found in association with the undernutrition. One patient was convalescent from acute rheumatic fever and showed evidence of an endocarditis which was apparently quiescent during the period of observation. Low grade pyelitis and cystitis were present in several of the women. Subacute or chronic pharyngitis was frequent. One patient suffered from chronic colitis. Another, a girl with a severe degree of undernutrition, had ptosis of a kidney accompanied by severe pain but without infection. In general it might be said that these patients were very prone to low grade infections which could not be broken up. Although in several of the hospital patients, acute febrile states were present at the outset, the records presented cover the afebrile and convalescent periods. The office patients were likewise frequently the subjects of persistent low grade infections, although in many cases these infections were not as severe as in the hospital group.

Results of Treatment

No data are available regarding the intakes of the office patients. Although a high caloric diet was calculated for many of them, the diet was only measured in most instances and, where the patient actually weighed the food, the figures are of only relative merit. Of the 18 hospital cases, complete dietary data are available for 16. The detailed analysis of these diets will be presented later.[62] It is of interest to note that the average caloric intake for the group was 3320 calories. With the exception of the absolutely low but relatively high figure, 2310 calories, in the case of the ten year

old patient, the lowest intake was 2790 calories. The highest average figure was 5090 calories. Thirteen of the 16 diets fell between 2800 and 3450 calories. This range of figures represents, therefore, the level of intake at which a significant rate of weight gain may be expected.

The weight changes which were observed have been arranged in tables 1 and 2. In the office group the increases varied from a minimum of 3.7 kilograms to a maximum of 14.3 kilograms. The average for this group was 8.2 kilograms. The hospital patients showed an average weight increase of 5.9 kilograms with a range from 1.7 kilograms to 17.7 kilograms. The average increase for the 39 patients was 7.1 kilograms. These figures are of considerably more interest when regarded from the point of view of body stature. Although at the outset the patients of the hospital group were 26 per cent below their ideal weights and those of the office group 22 per cent, after treatment the figures were 16 per cent and 9 per cent respectively. All but seven of the office group came well below the defined limit of undernutrition, whereas six of the hospital group were below this 15 per cent level. Again these data may be examined with reference to the change which was produced in the organism by the weight increase. After the dietary period, the hospital group patients had increased their bodies by 13 per cent of the initial mass and the office group patients by 17 per cent. Stated in other words, these patients increased their body mass by roughly one-seventh in these short periods. When expressed in relation to the time factor these figures acquire greater significance. It cannot be too frequently emphasized that the acquisition of a significant weight increase requires weeks and even months. In the office series the patients adhered to the program for from five to 16 weeks, on the average 10.9 weeks. In this average period of more than 2.5 months, they gained a total of 171.9 kilograms or on the average 8.2 kilograms per person. The rate of weight gain was, therefore, .78 kilograms per week. The 18 hospital patients gained a total of 106.2 kilograms or 5.9 kilograms per person. This was, however, accomplished in only five weeks (range two to 13.5 weeks) which gave a rate of change of 1.13 kilograms per week. Again, as above, these data may be restated to express the change which took place in the body. It was found that the office group changed their mass at the rate of 1.6 per cent per week while the hospital group averaged 2.8 per cent per week. Special attention may be directed to patient number 6 who increased his body at the rate of 7.1 per cent (or 1/14) per week for six weeks. This patient fell just short of a 50 per cent increase in body weight in a month and a half. Changes of body substance of these magnitudes of necessity require readjustments in body metabolism. The changes which were observed in certain aspects of metabolism will be described in subsequent papers.

The effects of treatment upon the symptomatology of the patients were striking. Practically all of the initial complaints entirely disappeared. The circulatory distress uniformly diminished and the irritability and nervous tension were appreciably improved. The thyrotoxic patient gained 9.1 kilo-

TABLE I
Office Series

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Pt.	Age Yrs.	Sex	Height In.	Ideal Wt. Kilo	Initial Weight		Duration Weeks	Final Weight		Weight Increase		Rate of Change	
					Kilo	Under Wt. %		Kilo	Under Wt. %	Kilo	%	Kg./ /Wk.	%/ /Wk.
A	30	F.	67	64.4	53.9	16	7	63.7	1	9.8	18	1.40	2.6
B	50	M.	69¼	75.3	57.6	24	12	67.1	11	9.5	16	.79	1.4
C	22	F.	69¼	65.8	55.4	16	13	67.2	+2	11.8	21	.91	1.6
D	25	F.	65¼	59.9	50.8	15	11	58.7	2	7.9	15	.72	1.4
E	51	F.	65	67.1	48.1	28	12	58.5	13	10.4	21	.87	1.8
F	52	F.	61¼	61.7	40.1	35	10	47.5	23	7.4	18	.74	1.8
G	25	F.	65	59.4	42.6	28	11	56.9	4	14.3	34	1.30	3.0
H	48	M.	72¼	83.9	63.1	25	9	70.5	16	7.4	12	.82	1.3
I	61	M.	68	74.0	59.0	20	11	63.1	15	4.1	7	.37	.6
J	26	F.	67	63.1	50.6	20	13	58.6	7	8.0	15	.61	1.2
K	42	F.	67¼	68.5	60.3	12	12	69.1	+1	8.8	14	.73	1.2
L	52	F.	67¾	72.6	54.9	24	8	61.5	15	6.6	12	.83	1.5
M	24	M.	66½	64.4	56.2	13	7	59.9	7	3.7	7	.53	.9
N	28	F.	64¾	59.9	50.0	16	15	56.5	6	6.5	13	.43	.8
O	33	F.	64	60.3	41.7	31	5	46.3	23	4.6	11	.92	2.2
P	42	F.	59	57.6	35.4	39	9	46.5	19	11.1	31	1.23	3.5
Q	45	F.	59	58.1	39.2	33	16	48.1	17	8.9	23	.56	1.3
R	27	F.	61¾	55.4	49.2	11	11	55.6	0	6.4	13	.58	1.2
S	32	F.	66¼	64.0	49.7	22	11	59.9	6	10.2	21	.93	1.9
T	34	F.	66¼	64.4	52.8	18	14	61.8	4	9.0	17	.64	1.2
U	36	F.	66¼	64.9	55.1	15	11	60.6	7	5.5	10	.55	1.0
Ave.	37		65½	65.0	50.7	22	10.9	58.9	9	8.2	17	.78	1.6

TABLE II
Hospital Series

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pt.	Age Yrs.	Sex	Height In.	Ideal Weight Kilo	Initial Weight		Ave. Caloric Intake Cal.	Duration Wks.	Final Weight		Weight Increase		Rate of Change	
					Kilo	Under Wt. %			Kg.	Under Wt. %	Kg.	%	Kg./ /Wk.	%/ /Wk.
1	32	F.	64	59.8	41.9	30	2790	13½	53.3	11	11.4	27	.84	2.0
2	10	M.	51¾	29.0	21.2	27	2310	3	22.9	21	1.7	8	.57	2.6
3	32	F.	62½	56.7	38.9	31	2850	3	44.1	22	5.2	13	1.73	4.4
4	22	F.	62	54.0	43.1	20	3200	4	47.5	12	4.4	10	1.10	2.5
5	28	M.	66	64.4	49.5	23	2980	6	54.3	16	4.8	9	.80	1.6
6	35	M.	68	71.3	41.4	42	5090	6	59.1	17	17.7	43	2.95	7.1
7	24	F.	62	54.9	40.9	25	3280	12	52.9	3	12.0	29	1.00	2.4
8	20	F.	62½	54.0	44.0	19	—	2	45.7	15	1.7	4	.85	1.9
9	31	F.	64¾	60.8	47.6	20	3430	2	49.9	18	2.3	5	1.15	2.4
10	23	F.	66¼	59.9	44.6	26	3200	4	48.9	18	4.3	10	1.08	2.4
11	15	F.	59	48.1	34.7	28	—	3	36.9	23	2.2	6	.71	2.0
12	33	F.	63	58.5	35.1	40	3310	8	42.2	28	7.1	20	.89	2.5
13	33	F.	63	58.5	39.5	32	3450	3	43.0	26	3.5	9	1.17	3.0
14	26	F.	64¼	58.1	49.4	15	3060	3	54.8	6	5.4	11	1.80	3.8
15	25	F.	67	62.6	46.6	25	3260	5	52.8	16	6.2	14	1.24	2.7
16	25	F.	67	62.6	54.1	13	3310	4	59.0	6	4.9	9	1.23	2.2
17	22	F.	64¼	57.2	46.7	18	2800	2½	49.0	14	2.3	5	.92	1.9
18	33	M.	66½	66.7	46.4	30	4790	7	55.5	17	9.1	19	1.30	2.8
Ave.	26		63½	57.6	42.5	26	3320	5	48.4	16	5.9	13	1.13	2.8

grams, and was relieved of many of his symptoms but his basal metabolic rate remained high and it was felt desirable to operate. The response of the patients with low grade infections was almost uniformly favorable. The frequency of colds diminished. Two cases of chronic colitis became free of symptoms.

It should not be assumed that a person who habitually has eaten 2000 calories per day or less can suddenly change to a 3000 calorie intake without a certain amount of physiological reaction. For the first few days practically all patients must literally force themselves to ingest the additional food. It should not be inferred that because a mechanical load was thrown on the gastrointestinal tract the digestion or absorption of food was defective. Quite the contrary was the case as will be shown later. A particular load appeared to be thrown upon the circulation not only to supply blood to the abdominal viscera but also to dissipate the extra heat which the meal produced. These and similar readjustments produced sensations which were often unpleasant. The sensations could be minimized by careful observation of the rest periods as described. This discomfort which the patients experience must be borne, though for only a few weeks, as the price which they must pay for the return to health.

It was mentioned above that two of the hospital patients failed to respond to treatment. One of these patients had dementia praecox. Although an adult of moderate frame this patient weighed only 75 pounds. No amount of pressure could induce the ingestion of even a maintenance diet. According to a subsequent report this patient died several months later, having a final weight of around 60 pounds. The second failure occurred in a young woman with probable multiple sclerosis who could not be induced to eat more than a maintenance diet. The failure of these patients to respond to dietary treatment resulted entirely from their inability to eat the prescribed diet.

Four of the patients described above have had repeated periods of observation. The two hospital patients 12 and 15 were treated for eight and five weeks respectively in preparation for necessary pelvic operations. Several weeks after their operations they were again placed on the high caloric regimes for periods of three and four weeks respectively. From the data listed in table 2, it may be seen that the rates of weight gain in both preoperative and postoperative periods differed in no essential detail. Of the office series, patient P followed the regime for nine weeks during which she gained 11.1 kilograms. Three years later she returned for treatment (Q) and in 16 weeks gained 8.9 kilograms. Patient S gained 10.2 kilograms after 11 weeks of treatment. Two years later (T) she gained 9.0 kilograms in 14 weeks and again two years later (U) she gained 5.5 kilograms in 11 weeks. Both of these women were mature and of considerable force of character. They were, however, unable to establish permanently new habits of eating. The prompt restoration of weight when the regime was reapplied indicates the absence of any unusual phenomenon. The progressive diminution in the weight gains of successive periods suggests the inability of these per-

sons to make the same inevitable sacrifices in the interests of weight gain a second and a third time although in both cases excellent records were attained on the first admissions.

The permanence of the weight gains which have been secured is a matter of considerable interest. Only a few of the subjects of the hospital series could be followed for more than a year. Three of the patients (8, 10, and 11) are known to have lost their increases in weight. These three young women, who were quite typical of a large number of undernourished patients, were pampered persons who, yielding to family pressure, agreed to put on weight in the interests of health. These subjects gained as rapidly as the others during their periods of hospitalization. They followed the program outlined for only short periods after the two to four week stay in the hospital. Two other patients (15 and 18) have been followed for two and three years respectively. They followed the regime for more than nine and seven weeks during which they gained 11 and 9 kilograms respectively. After discharge they continued to follow instructions until they had far exceeded their ideal weights. They have maintained weights which are roughly 5 per cent greater than their ideal weights quite without effort for the periods noted. In the office series, only four patients have been lost from observation. Nine patients have maintained their weight changes for periods of one or more years. In the majority of these patients there has been a complete relief of the presenting symptoms. Five patients have failed to hold their new weight levels. In each case a return to the old habits of life could be held responsible. The records of patients P and S have been reviewed above. The histories of these patients emphasize the principle which we believe constitutes the basis for satisfactory treatment and permanence of weight gains. If a patient himself honestly wishes to improve his weight and if he has the strength of character to stand the distress and restrictions which are inevitable during the first few weeks of the regime, a permanent weight gain of any desired magnitude can be secured.

Summary

1. Undernutrition may be regarded as the result of a food intake which is inadequate in comparison with the energy output. The evidence which has been advanced in support of specific etiologic factors, such as heredity, endocrine dyscrasias, and central nervous system disorders, fails to prove that the structural or functional abnormalities which have been observed are the cause of the undernutrition.

2. By the use of measures which produced an adequate positive energy balance, a series of patients representing various types of acute and chronic undernutrition has gained weight both in office and in hospital practice.

3. An adequate positive energy balance was secured not only by a high caloric intake but also by a reduction of energy output by a strict program of living.

4. As a result of the use of this method of treatment over a period of

four years, 21 office patients have averaged a weight increase of 8.2 kilograms in 10.9 weeks or .78 kilograms per week. Eighteen hospital patients have gained on the average of 5.9 kilograms in 5 weeks or 1.13 kilograms per week.

5. The correction of undernutrition in the patients described resulted in the disappearance of many diverse symptoms, an increased feeling of well-being and more especially an increased resistance to fatigue and to infection.

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ULTRAHIGH FREQUENCY PYRETOTHERAPY OF NEUROSYPHILIS*

A Preliminary Report

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IT IS NOW generally agreed that fever is essentially a protective and defensive mechanism. It is known that the fever which accompanies infection exerts an adverse influence upon the growth of bacteria, diminishes the potency of toxins, favors phagocytosis, and stimulates the development of immune bodies.[1] The gradual abandonment of antipyretic drugs has naturally followed the recognition of these facts. More effective physical agents are now utilized to combat extreme hyperpyrexia.

The monumental researches of Wagner-Jauregg introduced artificially-induced fever as an important addition to the therapeutic armamentarium against many chronic afebrile diseases. The remarkable results which have been achieved with pyretotherapy in cases of general paresis, tabes dorsalis, diffuse central nervous system syphilis, and asymptomatic neurosyphilis leave no doubt as to the urgent need for the wider application of this form of treatment, particularly to the early stages of the disease with a view to preventing the late serious consequences. The purpose of the present investigation, now in its preliminary phase, is to determine whether or not fever therapy can forestall the disastrous late effects of syphilis.§

The fact that similar results have been obtained following the employment of a wide variety of fever-inducing agents (malaria, rat-bite fever, relapsing fever, typhoid vaccine and other foreign proteins, hot baths, hot air, electric blankets, diathermy, and radiothermy) indicates that the com-

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This investigation was made possible by a grant from the Charles F. Kettering Foundation.

Presented at the Seventeenth Annual Clinical Session of the American College of Physicians, Montreal, February 8, 1933.

† Doctor Kislig died on February 7, 1933.

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§ This investigation had its inception in ideas expressed in a book by Paul de Kruif, Ph.D., entitled "Men Against Death," Harcourt, Brace and Co., N. Y., Chapt. 9, pp. 267–279.

mon denominator of all of these methods—fever production—is largely, if not entirely, responsible for the striking results which have been obtained.

The ideal method for the artificial induction of fever is one which is subject to complete control by the physician and which can be employed with safety and comfort to the patient. Despite the brilliant results which have been obtained with therapeutic fever following inoculations with malaria, rat-bite fever, and relapsing fever, the fact remains that the engrafted infection is capable of producing great damage, even death; may be difficult to control, and is inconstant in its fever-producing properties. It is rarely possible to achieve adequately effective febrile reactions with foreign protein substances, hot baths, and hot air.

In September 1929, Neymann and Osborne,[2] and in March, 1930, King and Cocke,[3] reported their experiences with artificial fever production with diathermy. Neymann and his collaborators [4] have reported that the remission rate in paresis treated with diathermy exceeds the results obtained in a comparative series of clinically similar cases treated with malaria or rat-bite fever. The results obtained by King and Cocke in the treatment of an unselected group of paretics compared favorably with those reported for carefully selected paretics treated with malaria inoculations. More recently, many other observers (Perkins,[5] Cortesi,[6] Wilgus and Lurie,[7] Prior,[8] Bishop, Horton and Warren,[9] Schamberg and Butterworth[10]) have found diathermy to be an effective method.

Since November 1931, we have been engaged in an investigation of the influence of an ultrahigh frequency field on neurosyphilis, gonococcal infections, arthritis, and vascular diseases of the extremities. The apparatus which we have employed for fever production was designed by Dr. Willis R. Whitney, director of the Research Laboratory of the General Electric Company. This apparatus has been adequately described by Whitney,[11] Carpenter and Page,[12] and DeWalt.[13] Whitney had observed that workers exposed to the high frequency field produced by short-wave radio transmitters developed fever. The essential difference between a 1-kilowatt radio transmitter used for transoceanic broadcasting and the apparatus used for therapeutic fever production is that the energy is concentrated between two large condenser plates instead of being directed from an aerial. The name " radiotherm " has been applied to the altered radio transmitter. The heating effect is produced by a vacuum tube oscillator, composed of two 500-watt radiotrons, producing a high-frequency field of approximately 10,000,000 cycles per second (30 meter waves) between the condenser plates.

The radiotherm differs from the diatherm used for fever production in that it operates at a frequency approximately ten times as great; the diatherm operates at a frequency of approximately 1,000,000 cycles (300-meter waves). The spark gaps of diathermy produce damped waves while the vacuum tube oscillator of radiothermy produces an even flow of continuous waves. In fever production by diathermy, alternating currents of

high frequency pass between large electrodes applied directly to the skin surfaces of the anterior chest wall, abdomen and back. If the electrodes are not maintained in direct contact with the skin surface, arcing occurs, resulting in skin burns. In fever production by radiothermy, the patient merely lies on a stretcher between the condenser plates; no electrodes are applied to the skin surfaces.

Early in the course of this investigation it became apparent that the comfort of the patient would be greatly enhanced by utilizing some form of insulated air-conditioned cabinet. This measure was necessitated by the fact that short radio waves are concentrated in the drops of sweat which accumulate on the skin surface, producing arcing and burning. We found that the practice of wrapping the patient in many blankets, or using small hair-dryers in inadequately insulated cabinets, did not prevent arcing.

With the coöperation of Mr. Charles F. Kettering, director of the Research Laboratory of the General Motors Corporation, and the engineers of the Frigidaire Corporation, we have developed a highly efficient air-conditioned cabinet in which the nude patient lies, with his head extending outside the cabinet. The condenser plates are contained in the side walls of the cabinet. By passing a column of heated air (500–1000 cubic feet per minute at 150–200°F. or 66–93°C.; relative humidity, 0–10 per cent) over and under the patient, it is possible to dissipate sweat as it reaches the skin surface. The incorporation of recirculation ducts makes it possible to reutilize any quantity of the heated air. This refinement prevents arcing and adds enormously to the safety and comfort of the patient. The high temperature of the air is well tolerated because of its rapid movement and low relative humidity.

While the air-conditioned cabinet which we are now using appears to be eminently better than any other similar apparatus now available, we are not convinced that we have as yet perfected the method. We are now endeavoring to develop a much simpler and much less costly cabinet, with a view to further increasing the comfort of the patient. Furthermore, the high cost and the complexity of the vacuum tube oscillator, as now employed for fever production, and the relatively short life of the expensive radiotrons, have impressed us with the urgent need for the development of a cheap and simple fever-producing apparatus, which will eliminate the discomfort and hazards of the contact electrodes used in diathermy, and which will permit adequate air-conditioning and the employment of recording temperature devices.

Ordinarily it requires from 30 to 60 minutes to raise the rectal temperature from the normal level to the desired height (105–106°F. or 40.5–41.1°C.). The mouth and rectal temperatures, pulse and respiratory rates are recorded before the treatment is begun, and every 10 to 20 minutes during the course of the treatment. Because of the fact that there is no uniformity in individual response to fever production by high frequency methods, treatment must be strictly individualized. It is our practice to

proceed cautiously until we have determined each individual's reaction. During the first treatment, temperature readings are made every 5 or 10 minutes. Blood pressure determinations are made before the treatment, when the desired fever level is reached, at the end of the sustained febrile period, and when the temperature has reached the normal level. We have found the rectal temperature to be much more reliable than the mouth temperature. Since the available recording thermometers cannot be used in an electrostatic field of such intensity, mercury thermometers are employed. After the history, physical examination, and laboratory studies have determined eligibility for this form of therapy, the patient is asked to eat a light breakfast on the morning of each treatment. Several patients have been given amytal or paraldehyde by mouth 20 to 30 minutes before the treatment is commenced. If unusual restlessness and apprehension ensues, morphine is given by injection. Many patients, particularly after the first one or two treatments, require no sedatives.

We have observed the following contraindications in the employment of sustained artificial fever: advanced age, myocardial or renal insufficiency, active tuberculosis, aortic aneurysm, or rapidly progressive late neurosyphilis. The complexity of the various forms of high frequency apparatus in the present state of their development makes it imperative that their employment for therapeutic fever production should be restricted to hospitals, under the direct supervision of a physician who has thoroughly familiarized himself with the physical and technical principles involved. Furthermore, only adequately trained nurse-technicians should be entrusted with the responsibility of giving the treatments.

Until recently we have maintained the fever temperature produced by the radiotherm by covering the patient with heated blankets and transporting him rapidly to a warmed bed in an adjacent room. Here the patient was wrapped in two heated blankets, outside of which were placed eight " Hotpoint " flexible rubber electric pads. Four or five blankets were then placed outside the heater pads. With this procedure it is ordinarily possible to maintain the temperature at the desired level for the remainder of the five-hour period. The advantage of the constant heat production by rubber electric pads over hot water bottles is obvious. For several months we have also successfully maintained fever in insulated, moisture-proof electric blankets.

Even though the hazard of arcing is removed by this practice, many patients have complained of the heat in the secondary maintenance pack while they have voiced no objection to the heated air in the cabinet during the elevation of temperature with the radiotherm. The patient perspires freely in the pack; consequently the body is exposed to high relative humidity as well as to high temperature. To avoid this situation we are now permitting the patients to remain in the air-conditioned cabinet throughout the five-hour febrile period. The passage of the column of heated air, without the use of the radiotherm current, around the patient's nude body

is sufficient to maintain the temperature at the desired level. After the flow of high frequency current is stopped the rate of air flow is decreased and the vapor content of the air increased. Patients who have been subjected to both methods of temperature maintenance are grateful for the change to the cabinet-maintenance method. The temperature of the moving column of heated air is so much greater than the body temperature that there is no loss by radiation. The temperature of the column of air can be controlled readily to conform to the individual's tendency to attain a higher or lower temperature than that desired. If the patient's temperature should exceed the therapeutic limit of safety (106.8°F. or 41.5°C.) the temperature may be promptly lowered by reducing the air temperature of the cabinet.

Up to the present time we have completed the course of treatments of 100 patients. Each patient has received 10 treatments.* Each treatment has consisted of five hours of sustained fever, at weekly or biweekly intervals. With the exception of a few small first- and second-degree skin burns in those patients who were treated prior to the installation of the air-conditioned cabinet, no person has been injured during the 1000 treatments (5000 treatment hours).

While constant competent nursing attention is required throughout the entire treatment, the adoption of the air-conditioned cabinet for fever production and maintenance has greatly simplified this problem. One radiotherm machine, on wheels, can be used for the initial fever production of several patients by using several cabinets. By gradually lowering the temperature of the air in the cabinet after the febrile period is ended, the patient's temperature can be brought to approximately the normal level before he is removed from the cabinet.

We have learned that the sense of exhaustion commonly experienced by many of our patients early in the course of this investigation can be largely overcome by supplying large quantities of chloride-containing fluids. We discovered that most patients lost between three and five liters of sweat during the five-hour febrile period. The supplying of four to five liters of water during and immediately after each treatment satisfied the thirst, but did not favorably influence the symptoms of exhaustion; in fact, they appeared often to be augmented. A study of the blood chemical analyses revealed that while the creatinine, urea nitrogen, uric acid, sugar and calcium values showed the slight anticipated rise due to concentration of the blood and the increased metabolism of fever, the blood chloride values exhibited an average decline of 40 mg. per cent at the end of the febrile period in approximately 80 per cent of the patients. In five instances the fall exceeded 100 mg.; one of these patients developed typical hypochloremic tetany during the fifth hour of treatment. Some patients experienced nausea, vomiting, abdominal cramps, or muscular twitchings.

* Patients with gonococcal infections, arthritis or vascular diseases of the extremities usually require fewer treatments.

Chemical analysis of the sweat revealed an average sodium chloride content of 650 mg. per cent. It became apparent that from 20 to 26 grams of sodium chloride were being withdrawn from the blood and tissues during each treatment. Gastric analyses, made at thirty-minute intervals during the febrile period, indicated that the free hydrochloric acid completely disappeared during the first 30 to 90 minutes. The combined acid exhibited a decided, but less complete, decline. A study of the urinary chlorides yielded less constant data.

These findings suggested the advisability of supplying chlorides during and immediately after each treatment. It was immediately apparent that the ingestion of four to six liters of 0.6 per cent sodium chloride solution largely abolished the sense of fatigue and exhaustion and practically eliminated nausea, vomiting, abdominal cramps and muscular twitchings. We have found the instillation of saline solutions per rectum to be much less effective.

The practice of replacing chlorides lost in the sweat has produced an apparently beneficial influence upon the blood chloride content; the majority now show no appreciable change in blood chloride values during or after the treatment. During the first few months of this investigation it was our practice to retain patients in the hospital for at least 24 hours following each treatment. Since the institution of the chloride-replacement regimen, eight months ago, it has not been necessary to keep patients in the hospital longer than one or two hours after the temperature has reached the normal level. This is particularly important in the management of early syphilis, where hospitalization would provide an insuperable obstacle to the general application of this form of treatment.

While we have obtained gratifying results in the treatment of gonococcal infections, certain forms of infectious arthritis, and vascular diseases of the extremities, we have largely centered our efforts on the application of this form of therapy to syphilis. Carpenter and Warren,[14] Hinsie and his collaborators,[15] and Tenney [16] have employed radiotherm pyretotherapy in the treatment of various forms of neurosyphilis and have found that the percentage of complete remissions and improved cases compares most favorably with the results obtained with malaria therapy. Many observers (Kyrle,[17] Matuschka and Rosner,[18] Kauders,[19] Paige, Rickloff and Osborne,[20] Neustaedter,[21] Gugenheim,[22] Reese,[23] Solomon and Epstein [24]) have found malaria fever therapy plus specific chemotherapy to be much more effective than fever therapy alone. For this reason we have combined specific treatment (bismarsen, iodobismitol or tryparsamide) with the radiotherm treatments. Kyrle achieved remarkable results with both early and late syphilis by interposing the malaria-induced fever between two courses of salvarsan therapy. Kyrle concluded that therapeutic fever was much more effective when there was available a depot of salvarsan in the tissues. One great difficulty with the combination of malaria therapy with arsenicals is that the injection of the arsenic-containing drug usually inactivates the

malarial infection. With high frequency fever it is possible to combine the two throughout the course of fever treatment. This has been our practice. We have continued the specific treatment (weekly injections) for at least four months following the last fever treatment. Furthermore, if it should appear to be advisable to repeat the artificial fever treatment, the likelihood of successful fever production with a second or third inoculation with malaria is remote. With high frequency fever therapy this handicap is entirely removed.

Hinsie [15] has subjected paretics to 70 hours (10 treatments of seven hours each) of radiotherm fever on the basis of the observation that 25 patients with general paresis obtained complete remissions after 70 hours of malaria-induced fever above 102°F. (38.9°C.). The conclusion of Wagner-Jauregg that eight malarial chills should be considered an optimum, rather than the 16 chills formerly employed, led us to reduce the number of hours of fever to 50. The fact that many of our patients appeared to experience the most marked improvement after the first six or seven treatments leads us to believe that 30 to 40 hours of fever might be equally beneficial in some individuals. We intend to investigate further this possibility.

Of the 100 patients who have received radiotherm treatments, 36 were treated for some form of neurosyphilis. All of these patients were selected because of the failure of vigorous specific therapy to accomplish favorable results. Twelve of these refractory patients satisfied the diagnostic requirements for general paresis, five were taboparetics, five were tabetics, four had diffuse central nervous system syphilis, six had asymptomatic neurosyphilis, and four had congenital syphilis involving the central nervous system.

The scope of this communication permits only a summary of the results attained. None of the paretics had the disease in a sufficiently advanced form to require committment to a hospital for the insane. Of the 12 early paretics all but one had a complete remission of all clinical symptoms at the conclusion of the combined radiotherm-specific therapy treatments; the other patient was considerably improved. Marked improvement in the intellectual sphere was ordinarily observed after the first two or three treatments. The psychic improvement was accompanied, with one exception, by decided gain in weight and strength. The usual remark of the patients—"I feel like a new man"—was obviously justified by clinical observations. Two patients with presumably well-marked optic atrophy experienced remarkable improvement in vision.

The spinal fluid Wassermann and Kahn reactions were reversed to negative in three instances, became less positive in seven, and remained positive in two, at the end of the combined course of treatment. In one the serologic reaction became negative during the next six months. The delay in serologic response to malaria therapy in some successfully treated cases of paresis has been reported by many. The cell count and albumin content of

the spinal fluid returned to the normal level in every instance. The colloidal gold curves became negative in three instances; in seven others they were appreciably lowered; in one instance there was no change; in one instance a first zone curve was elevated. The failure of the colloidal gold curve to exhibit constant relationship to clinical improvement is the usual observation following malaria therapy. Furthermore, the serologic findings do not parallel the degree of clinical improvement, particularly in late paresis. All but one of the paretics in this series are now engaged in their customary occupations.

In the five taboparetics, the most important observation has been the rapid improvement in mental orientation and the prompt subsidence of root pains. In four of the five cases, severe gastric crises or lancinating pains, or both, were the dominant feature of the disease; all were promptly relieved of the intense pain. One patient in this series had developed a recurrence of symptoms six months after malaria therapy (without specific therapy). The spinal fluid formulae showed essentially similar responses as in the paretic group. The pleocytosis and the increased organic solids were promptly reduced to normal levels. The Wassermann and Kahn reactions were reversed to negative in two instances, became less positive in two, and remained negative in another. No patient has experienced a recurrence of root pains during the period of observation (3 to 15 months).

In the tabetic group of five patients, ataxia (in all) and lancinating pains (in three) were the chief complaints. In one case in which periodic root pains had occurred for two years, and in which a typical tabetic gait had developed two months before the fever treatments were instituted, there occurred prompt disappearance of the lancinating pains (after the first treatment) and the tabetic gait (after the third treatment); neither has recurred since treatment was begun one year ago. In another case in which the tabetic gait had existed for approximately a year, considerable improvement in the ataxia was obtained; lancinating pains were promptly abolished in this case. In one case, with lancinating pains and a tabetic gait of two years' duration, no improvement in gait has occurred, but the patient is grateful for complete relief of the root pains. In two cases with ataxia of long duration (four and seven years), no improvement in gait was obtained, but both patients gained in strength and weight; in one the symptoms of "cord bladder" disappeared after the fourth treatment. The spinal fluid Wassermann and Kahn reactions were reversed to negative in one instance, became less positive in one, and remained negative in three.

In the group of patients with diffuse central nervous system syphilis were placed those who had various manifestations of symptomatic neurosyphilis, which could not be definitely classified as paresis, tabes, or taboparesis. The average age of the patients in this group was 30 years (13 years younger than the average age of the paretics, tabetics and taboparetics). All experienced neuro-recurrence following presumably adequate specific therapy. The average duration of syphilitic infection was seven

years, as contrasted with average duration of 15 years in the paretic, tabetic and taboparetic groups. All presented clinical and cytologic evidence of well-marked syphilitic meningitis. The cell counts and organic solids of all had reached the normal level at the conclusion of the fever treatments. The spinal fluid Wassermann and Kahn reactions became completely negative in three instances and less positive in two recently observed cases. The ocular complications of exudative uveitis in one case, multiple ocular palsies in another case, and active choroiditis in another patient, were arrested.

The response of the six patients with asymptomatic neurosyphilis was uniformly favorable. The only manifestation of neurosyphilis in this group was the presence of positive reactions of the spinal fluid. Even though asymptomatic neurosyphilis often occurs in early syphilis, none of our patients in this group has had the disease less than three years (average 4.5 years). In all five, the Wassermann and Kahn reactions of the spinal fluid were negative at the conclusion of the course of fever-specific therapy treatments. The cell counts and quantitative organic solids determinations were reduced to normal limits.

The response of many congenital syphilitics, with neuraxis involvement, to specific therapy is often practically nil. Our experience with four such cases provides hope for the future management of these refractory patients. The ages of these patients were 7, 12, 16 and 20 years. Two were classified as juvenile paretics on the basis of the spinal fluid formulae, while the other two were regarded as cases of diffuse central nervous system syphilis. Two patients were treated during active interstitial keratitis; all signs of keratitis disappeared without evidence of scarring after one five-hour fever in one case; the keratitis became more gradually inactivated after five treatments in the other case, with small residual opacities. The cell count and albumin content promptly declined to normal. The spinal fluid Wassermann and Kahn reactions were reversed to negative in one instance, became less positive in two, and remained negative in one. All are now in the remission stage as regards the clinical symptomatology.

While we are encouraged by the striking clinical and serologic improvement in this small series of patients, we realize that the time of these remissions is still too short to justify drawing any conclusions regarding their permanence. In view of the treacherousness of this infection, we intend to exert every effort to follow the progress of these patients throughout the balance of their lifetime.

A recent survey conducted by Clark[25] indicates that each year some 423,000 persons in the United States seek treatment for early syphilis. Since it has become more generally appreciated that examination of the spinal fluid as a routine measure is an indispensable part of the management of early, as well as late, syphilis, it has become apparent that at least one-third of persons with syphilis of less than two years' duration show some evidence of neurosyphilis. When changes characteristic of central nervous system invasion occur in the spinal fluid, the effect of treatment on the spinal fluid

formula becomes the first consideration in the subsequent management of the disease. Vigorous continuous specific therapy is often ineffective in arresting the progress of neurosyphilis. The remarkable results obtained by Kyrle,[17] Wile and Davenport,[26] O'Leary,[27] Gugenheim,[22] Gougerot [28] and others in the treatment of asymptomatic neurosyphilis with malaria leaves no doubt of the challenging fact that the best time to treat paresis and tabes is before they develop to that stage. The results obtained in early neurosyphilis are eminently better than in the later stages of the disease.

More important than this observation, however, are the conclusions to be drawn from the brilliant results obtained by Kyrle in the treatment of syphilis during the first two years of its existence by the combined salvarsan-malaria-salvarsan regimen. The results were incomparably better than by any other method previously employed. Of 232 Wassermann-positive patients with early syphilis, the blood Wassermann reaction was favorably influenced in 230 (99.1 per cent) after a single combined course of treatment. Fifty-four of these patients exhibited Wassermann-positive reactions of the spinal fluid; all were reversed to negative and remained negative. When Matuschka and Rosner[18] reported upon the work of Kyrle, after his untimely death, not one of these patients had developed a positive Wassermann reaction in either blood or spinal fluid during the five years covered by this classical report.

On the basis of these observations, it seems logical to conclude that the ideal time for the institution of combined specific therapy and fever therapy is immediately following the establishment of the diagnosis of syphilis. We have now undertaken the treatment of syphilis in the primary and secondary stages by the combined ultrahigh frequency fever-specific therapy method. These observations will be made the subject of a later report. The advent of methods for the controlled and safe production of artificial fever should stimulate vigorous inquiry in this field.

Summary and Conclusions

1. The age-old conception that fever is a destructive process has given way to the modern knowledge that fever is a protective and defensive mechanism.

2. The value of artificially-induced therapeutic fever is now firmly established. Fever production appears to be largely, if not entirely, responsible for the results attained with a wide variety of fever-inducing agents.

3. The need for a method of artificial fever induction which can be employed with safety and comfort to the patient, and which is subject to complete control by the adequately-trained physician, is apparent. The induction of fever with an ultrahigh frequency oscillator (short-wave radio transmitter), known as the radiotherm, in conjunction with an efficient air-conditioned cabinet, appears to fulfill these requirements.

4. The symptoms of exhaustion and fatigue, and the occurrence of nausea, vomiting, abdominal cramps, and muscular twitchings during the

sustained fever treatments are apparently largely due to the great loss of chlorides in the sweat. These symptoms are practically eliminated by supplying large quantities of chloride-containing fluids.

5. One hundred patients with syphilis, arthritis, gonococcal infections, or vascular diseases of the extremities have been subjected by us to 5000 hours of sustained fever therapy without evidence of injury, except for superficial skin burns in some of the patients treated before the development of the air-conditioned cabinet.

6. With due regard to the relatively short time during which our patients have been under observation, it may be stated that the results obtained with combined specific therapy and radiotherm pyretotherapy in cases of neurosyphilis are at least comparable to the results obtained with the more hazardous malaria-specific therapy regimen.

7. The fact that the most brilliant results are achieved in cases of early neurosyphilis, together with the remarkable observations of Kyrle in the treatment of early syphilis with the more hazardous, unreliable and time-consuming malaria-specific therapy regimen, make it probable that the logical time to institute combined fever and specific therapy is immediately following the establishment of the diagnosis of syphilis.

Note: Because of the necessity of following the progress of patients subjected to this form of therapy for many years, we are restricting our investigations to patients who live in Dayton or in the immediate vicinity.

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THE CLINICAL SIGNIFICANCE OF GASTRIC ACIDITY*

A Study of 6679 Cases with Digestive Symptoms

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IN 1886, Jaworski and Gluzinski [1] introduced the generally accepted system of estimating gastric acidity in terms of "degrees." They then pointed out that the subject had been intensively studied for over a hundred years and apologized for adding another communication to the many already published. Forty-six years later, Vanzant and her collaborators [2] called attention to the amazing fact that, despite the enormous amount of investigation, we have not even today any reliable standards of normal acidity for various ages. Their explanation that this gap in our knowledge is due in part to the difficulty of getting a large number of normals for study seems rational. All the previously reported studies of normals were made on comparatively small groups. Bloomfield and Keefer [3] studied 90 "normal" cases in one series and 30 in another. Other studies (Bennett and Ryle,[4] Apperly and Semmens,[5] Dahl-Iversen,[6] Moore et al,[7] Henderson [8] and others), were made on even smaller groups of young individuals, mostly college students. The methods used by various investigators varied widely.

The series reported from The Mayo Clinic comprises cases which were considered to be free from organic disease of the gastrointestinal tract, but they were not free from digestive disturbances. It is true that if we consider a person's digestion as normal only when he can eat with impunity anything within reason, in any quantity and at any time, very few people, especially those past middle age, could qualify as normal. The difficulties in studying normal acidity in the human are therefore manifold. Not only is it "not easy to get several thousand normal persons to submit to gastric intubation" (Vanzant et al), but it is doubtful whether any appreciable number of strictly normal persons could be found, particularly in the higher age groups, unless absence of gross pathology is accepted as the criterion of normality.

In discussing Vanzant's paper before the American Gastro-Enterological Association, in May 1931, one of us (J. L. K.) pointed out that our figures on gastric acidity collected from office and clinic patients, all of whom complained of gastrointestinal symptoms, corresponded to those of the

* Read before the American Gastro-Enterological Assoc. at Atlantic City, N. J., May 2, 1932.

Mayo group, collected presumably from normals. In perusing their paper, however, we find that our material resembles theirs more closely than was at first supposed. The cases of organic disease, which Vanzant excluded from her studies, constitute a large proportion in a hospital of the type of The Mayo Clinic, but are in a small minority in a gastrointestinal clinic for ambulatory patients or in the office of a gastroenterologist.

Inasmuch as it is practically impossible to secure perfectly normal individuals in the various age groups, the next best thing is to make a statistical study of large numbers. This communication is based on the study of a series of cases which we have been accumulating for the past twelve years. Our material lends itself to special grouping according to social status and partly to occupation, as well as to age and sex. We have also had the opportunity of following the gastric acidity in several individuals over a period of years, with results which, as far as we know, have not been reported in the literature.

Material

Of the 6679 test meals used as a basis for this communication, 2401 were performed at the Vanderbilt Clinic, 1062 in a clinic maintained by a labor organization of the needle trades, and the remaining 3216 on private patients in our respective offices. All the titrations at the Vanderbilt Clinic were carried out by the same technician, while the other tests were performed either by us or under our direct supervision.

Methods

All the patients received a Boas-Ewald test meal, slightly modified, namely four Uneeda biscuits and two glasses of water, the change from bread to crackers insuring more uniformity and greater convenience. A single extraction was made at the end of 45 minutes. For the titrations of free HCl and total acidity, Toepfer's reagent and phenolphthalein were respectively employed as indicators.

In classifying our cases in reference to acidity, we divided them into four major groups. Those showing no free HCl were classed as achlorhydria. Those showing free HCl under 20 degrees or total acidity under 40 were diagnosed subacidity. Those showing free HCl above 40 or total acidity above 60 were grouped as hyperacid. Thus, only those which had free HCl between 20 and 40 and total acidity between 40 and 60 were considered as "normal." A fifth group comprising a small number of cases, showing free HCl below 20 and total acidity above 60, we termed "dissociated acidity" and did not include in our basic tables.

We studied separately the data obtained in the clinic clientele from that of the office patients in an effort to detect any difference based on social and economic status. We also segregated for separate study a group of patients employed in the tailoring industry, almost all of them belonging to the Jewish race.

Inasmuch as the material studied is composed entirely of ambulatory cases as they appear in the gastrointestinal clinics and in offices of gastroenterologists and the proportion of patients with organic disease is comparatively small, the latter were included in our series. However, in order to determine the possibility of appreciable error, all cases of carcinoma, peptic ulcer and gall-bladder disease were excluded in a part of our material. The resulting percentage distribution and curves are practically the same as before the exclusions. (Tables 1 and 2.)

TABLE I

Age and Sex Factors in Gastric Acidity (2286 Cases)

	Percentages							
	Males—1402				Females—884			
Ages	*A*	*S*	*N*	*H*	*A*	*S*	*N*	*H*
11–20	2	20	26	50	0	22	48	30
21–30	2	15	36	46	3	25	46	24
31–40	2	9	33	55	7	27	36	29
41–50	3	8	26	61	13	22	42	22
51–60	5	20	24	50	15	21	34	29
61–70	20	8	20	52	20	16	20	44

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

TABLE II

Age and Sex Factors in Gastric Acidity after Organic Pathology Was Excluded

	Percentages							
	Males—1173				Females—766			
Ages	*A*	*S*	*N*	*H*	*A*	*S*	*N*	*H*
11–20	3	23	27	46	0	23	50	28
21–30	3	16	40	41	4	25	46	25
31–40	3	10	37	50	8	25	37	30
41–50	5	10	27	58	14	22	23	41
51–60	6	23	26	45	12	20	40	28
61–70	25	10	25	40	15	0	38	46

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

Wherever we encountered groups of less than 25, we did not consider them in plotting our graphs, as percentage calculations on small numbers are extremely unreliable and often incorrect. It is for this reason that figures below the age of ten are not included in our paper.

FINDINGS

The greatest relative number of patients at all ages up to 70 have high acid figures. (Figure 1 and Table 3.) Next in order are the moderate acidities (so-called normals), then the low and finally the achlorhydrias. The greatest percentage of high acidities is found in the fourth and fifth decades, gradually declining thereafter. The proportion of patients with

TABLE III

Gastric Acidity and Age (6679 Cases)

Decade	Cases	Per cent			
		A	*S*	*N*	*H*
11–20	216	2	23	32	43
21–30	1744	4	23	37	36
31–40	3141	5	19	32	44
41–50	1461	10	20	24	46
51–60	796	16	20	25	38
61–70	277	22	18	25	35
71–80	44	18	40	16	26

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

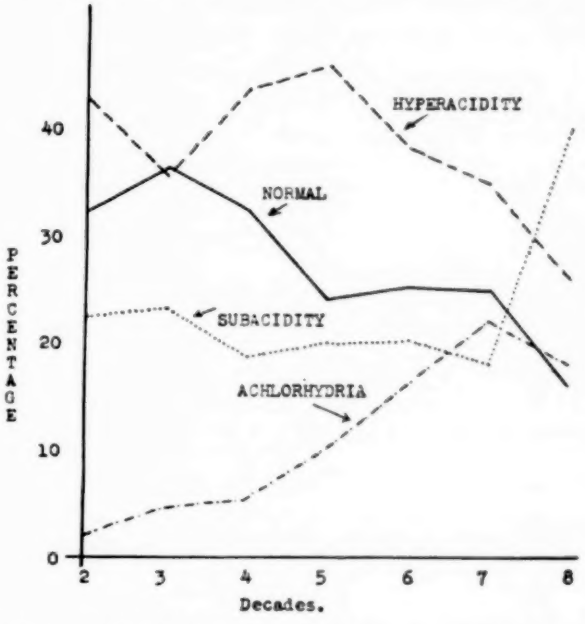

FIG. 1. Gastric acidity in relation to age. (6679 cases.)

what we are accustomed to consider normal acid figures slowly decreases from the third decade on. The low acidities fluctuate but little until the last decade when they show a definite rise. There is a progressive increase in the incidence of achlorhydria up to the age of 70, with slight diminution beyond that point. However, the number of cases in our series above that age is too small for positive statistical statements.

One group of patients, almost exclusively of the Jewish race and belonging to a labor union of the tailoring trades, showed a very high incidence of hyperacidities for all decades. As in the other groups studied, the peak was reached in the fifth decade, the entire curve being on a higher level. The other acidity curves were practically the same as in the other groups. (Table 4.)

TABLE IV

Gastric Acidity and Age; Needle Trades Group (1062 Cases)

Decade	Cases	Per cent			
		A	*S*	*N*	*H*
11–20	29	0	24	45	31
21–30	358	3	25	28	34
31–40	416	3	13	34	50
41–50	205	5	13	24	58
51–60	49	8	28	18	46
61–70	4	50	0	0	50

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

In a group of relatively wealthy private patients, the incidence and peak of high acidities were distinctly lower than in the working class group. (Table 5.)

TABLE V

Gastric Acidity and Age; Private Patient Group (2000 Cases)

Decade	Cases	Percent			
		A	*S*	*N*	*H*
11–20	65	2	31	29	38
21–30	500	5	32	32	31
31–40	595	5	28	31	36
41–50	417	13	27	22	38
51–60	277	17	25	25	32
61–70	114	25	25	23	27
71–80	24	12	54	8	25

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

The figures obtained on the Vanderbilt Clinic patients, presumably belonging to the poorer classes, of all races and creeds, showed acidities and curves between the extremes just described. (Table 6.)

TABLE VI

Gastric Acidity and Age; Vanderbilt Clinic Cases (2401 Cases)

Decade	Cases	Per cent			
		A	*S*	*N*	*H*
11–20	66	3	16	32	49
21–30	551	6	19	34	41
31–40	712	7	16	31	46
41–50	617	11	19	25	45
51–60	333	19	16	24	41
61–70	111	20	15	30	35
71–80	11	18	27	27	27

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

The generally recognized very high incidence of hyperchlorhydria in duodenal ulcer, and achylia or marked hypoacidity in gastric carcinoma is shown in table 7. The distribution in gall-bladder disease is the same as

TABLE VII
Gastric Acidity in Certain Diseases

	No. of Cases	Percentages			
		A	*S*	*N*	*H*
Gastric Carcinoma	41	45	40	10	5
Duodenal Ulcer	357	0	3	15	82
Gastric Ulcer	46	2	23	26	49
Gall-bladder Disease	247	9	28	32	31

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

that ordinarily found in the corresponding age periods.

The acidity means were calculated for each decade. (Figure 2.) The free and total acidities maintain a fairly constant level through the fifth decade when they show a gradual drop.

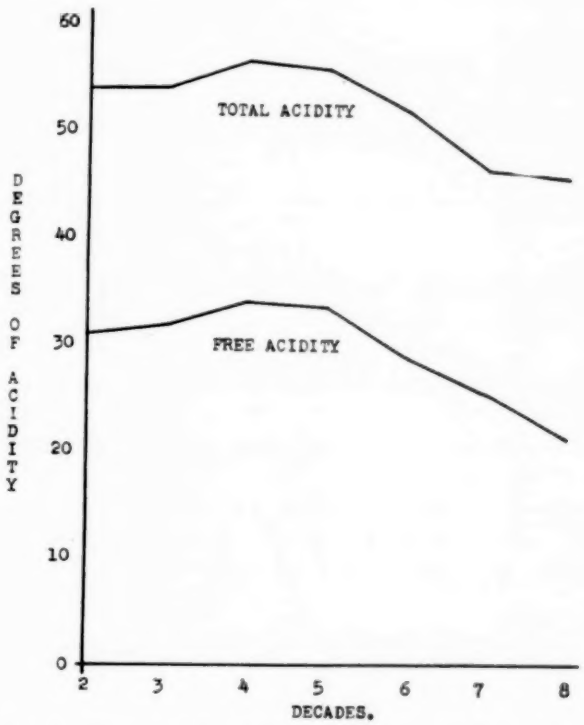

FIG. 2. Mean gastric acidity by decades. (6679 cases.)

As regards sex, we found, as did other investigators, that acidity in females runs generally lower than that in males. The difference corresponds to almost ten degrees in both the free and the total ranges. (Figure 3.)

In one series of 2000 cases, the dissociated acidity group was studied. Twenty-two cases were found, making an incidence of about 1 per cent.

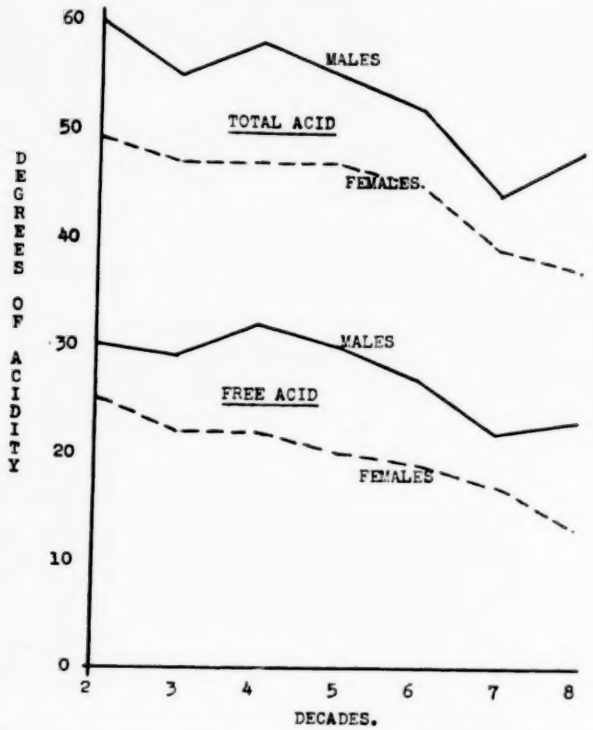

FIG. 3. Gastric acidity means in relation to age and sex.

TABLE VIII

Case 1

G. I. Neurosis—Fem.

Date	Age	Free HCl	Total Acid	Class
July 1922	42	8	16	*S*
July 1923	43	0	15	*A*
Dec. 1928	48	0	19	*A*

Case 2

G. I. Neurosis—Fem.

Date	Age	Free HCl	Total Acid	Class
June 1924	48	14	28	*S*
Sept. 1931	55	0	4	*A*
Apr. 1932	56	0	5	*A*

Case 3

Duodenal Ulcer—Male

Date	Age	Free HCl	Total Acid	Class
Oct. 1920	33	41	88	*H*
Apr. 1927	40	30	68	*H*
June 1930	43	32	66	*H*
Apr. 1932	45	18	58	*S*

Case 4

G. I. Neurosis—Male

Date	Age	Free HCl	Total Acid	Class
June 1925	78	11	33	*S*
May 1925	78	11	38	*S*
June 1929	82	2	15	*S*
Dec. 1930	83	2	19	*S*
Nov. 1931	84	0	7	*A*

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

The only remarkable feature noted was that ten cases in the group, or 45 per cent, suffered from gall-bladder disease.

The results of repeated test meals on the same individuals show several interesting features. In the first place a surprising constancy in the successive sets of figures is regularly obtained when the tests are performed under standardized conditions within relatively short periods of time, particularly in younger individuals. If the period of observation is prolonged to five years or more, especially after a decade, there appears a definite tendency, more so in older patients, to show a diminution or loss in acidity. (Table 8.) Thus, high figures become lower and low figures drop into the achlorhydria class. Exceptions, of course, do occur, as illustrated in the case of heterochylia in a neurotic individual, who, in the course of four and one-half years, had five analyses and managed to be in every class once and in the normal class twice. (Table 9.)

TABLE IX

G. I. Neurosis—Male

Date	Age	Free HCl	Total Acid	Class
1. Dec. 9, 1926	52	6	31	*S*
2. Dec. 9, 1927	53	38	58	*N*
3. Dec. 19, 1930	56	0	13	*A*
4. Feb. 28, 1931	57	32	61	*H*
5. Apr. 11, 1931	57	38	59	*N*

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

DISCUSSION

What Constitutes Normal Acidity. It is quite evident that we cannot accept one standard for all age periods. Some authors, especially those who have departed from the Boas test meal, digress from the usual normals of 20 to 40 degrees for free HCl and 40 to 60 for total acidity and name their own figures. Thus, Lerman,[9] using the alcohol and histamine test meal, considers the normal acidity range to be 20 to 70 degrees for free HCl. Bloomfield suggests that we dispense with the term normal and classify the cases as high, medium, low, and anacid.

The fact that some individuals are always achlorhydric and that the absence of free HCl was found in children (Wright,[10] Hertz,[11] Jacobsen,[12] and even in the newborn, Hess[13]) justifies the inference that lack of acid is a constitutional characteristic with some individuals and is "normal" for that particular type. Carlson[14] has long maintained that all grades of acidity as well as anacidity are found in a considerable number of "normal" individuals. Furthermore, it has been observed that a given type of gastric secretion is characteristic of certain families, high acidities being common in some and low acid figures or even achlorhydria in others (Dauwe,[15] Martinez,[16] Apperly and Norris[17]). In short, normality is generally a very elastic term. In the present state of our knowledge, it is evident that age

and sex must be considered in any discussion of normal standards. Utilizing the acidity means already referred to, it is an easy matter to construct a simple table, similar to that of height and weight or blood pressure, that might serve as a guide to the clinician in every-day practice. An arbitrary deviation of ten degrees on either side of the means would give the results in round figures, as shown in table 10. All cases falling within the above

TABLE X

Average Range of Acidity Distributed According to Age and Sex

	Free HCl		Total Acidity	
	Male	Female	Male	Female
11–20	20–40	15–35	50–70	40–60
21–30	20–40	15–35	45–65	35–55
31–40	20–40	15–35	45–65	35–55
41–50	20–40	10–30	45–65	35–55
51–60	15–35	10–30	40–60	35–55
61–70	10–30	10–30	35–55	30–50
71–80	10–30	5–25	35–55	30–50

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

limits could, therefore, be designated as moderate acidities (discarding the term normal), while others would be considered as high or low, as the case might be.

This table represents a rough scale somewhat more accurate than the old fixed forms in which age and sex were not considered, but without any pretense to such statistical accuracy as is manifest in the painstaking work of Vanzant and her collaborators.

Diagnostic Value of Gastric Acidity Determination. Inasmuch as all grades of acidity are found in healthy individuals, it follows that the diagnostic significance of acidity tests is only of secondary importance—it has only a confirmatory value. Thus, in the presence of achlorhydria, the evidence in favor of duodenal ulcer must be overwhelming to make the diagnosis. Likewise, a diagnosis of primary anemia would hardly be in keeping with high or moderate acid figures. At this point we wish to call attention to our observation that dissociated acidities (low free HCl and high total acidity) are suggestive of gall-bladder disease. The reason for the dissociation probably lies in the greater amount of duodenal regurgitation and higher combined acidity.

The Significance of Achlorhydria. The subject of achlorhydria has been discussed in great detail by numerous writers. Ehrman,[18] who introduced the conception of simple achylia, Martius,[19] Faber[20] and lately Bloomfield and his collaborators, as well as many others, have studied it from many angles. It is of particular interest as a possible predisposing factor to serious organic disease, such as gastric carcinoma and pernicious anemia. As precursors of carcinoma of the stomach, Hurst[21] puts achylia and gastritis in the first place. He cites two cases which were achlorhydric long before the

cancer developed. We have also had two cases which had no free HCl with negative roentgenological findings for six and eight years before they developed cancer of the stomach. Unfortunately, it is very rarely that patients with carcinoma of the stomach have records of previous test meals. The achlorhydria clinic which Bloomfield has inaugurated is therefore a step in the right direction and is worth emulating.

The Significance of Low and High Acidities. The increasing incidence of achlorhydria with advancing age suggests the probability that gastric acidity gradually fails with advancing years. The number of achlorhydrics is augmented by new recruits from among those with low acidities. The low acidity group is in turn replenished from the higher acidity groups. Some evidence of this was presented above. The process of decline does not seem to begin until the fifth decade is passed. In all of our groups, the greatest percentage of high acidities is found in the fifth decade. One may infer that probably our mode of living and dietary habits tend to stimulate gastric function, producing a greater proportion of high acidities up to that point. After the fifth decade, however, when all bodily functions are in the decline, gastric secretion also begins to diminish. The fifth decade thus constitutes a turning point and diminishing gastric acidity may be regarded as one of the indications of approaching old age, such as loss of hair and teeth, diminishing activity of internal secretions, arteriosclerosis, and so on.

On the other hand, high gastric acidity persisting into old age may be considered as an indicator of longevity. Only the hardier individuals reach the eighth and ninth decade and they seem to be the ones who have high gastric acidity. It is interesting to observe the contradictory reports as regards acidity in old age. Dedichen [22] and Davies and James [23] reported low acid figures, while Rafsky [24] found hyperacidity to be the rule in a group of exceedingly old individuals (70 to 90 years of age).

Practical Value of Test Meals. It is not within the province of this communication to enter into a discussion of the relative value of the many different test meals that were suggested in the past or are still in use. While the data reported here are based on results obtained with the single aspiration after a Boas-Ewald test meal, we do not wish to be misunderstood as advocating this method in preference to or to the exclusion of all others. For thorough discussion of the merits and drawbacks of the various procedures, the reader is referred to the writings by Boas,[25] Isaak-Krieger,[26] Andresen,[27] Garbat,[28] Gaither,[29] Smithies,[30] and others. Our feeling is that for practical purposes, it matters little what is used for a test meal or how many extractions are made. We would not even object to the use of fresh cabbage juice, as suggested by Orlowsky,[31] if one does not mind the trouble of procuring it in all seasons. Any test meal with a single aspiration will serve to classify the patient as to the type he belongs to, whether he secretes gastric juice of the high or low titre. It is only the exceptional case that will give low figures with one method and high ones with another.

It is now fairly generally accepted that with regard to gastric acidity

there are several types, differing constitutionally in the same manner as the sthenic and the asthenic, or the hypersensitive and the hyposensitive. From the standpoint of predisposition to various diseases it is very important to determine to which group the patient belongs and to classify him accordingly.

It is of importance to find out the low acidities as well as the anacidities, as it seems quite possible that the hypochlorhydrias are potential achlorhydrias and that the increase in achlorhydrias in the later decades is due to this factor. The importance of doing a test of the gastric secretory function on every patient cannot be overemphasized. One might go even further and say that it should be included in every periodic physical examination.

Any symptoms even remotely suggesting an early peptic ulcer should be considered seriously in the hyperchlorhydric and the patient kept under observation. On the other hand, it is known that pernicious anemia is preceded by achlorhydria long before any other suspicious evidence makes its appearance. Our knowledge of the achlorhydria preceding the development of gastric carcinoma is so far very limited and further investigation of this relationship is desirable.

It is also essential to know for dietetic considerations, the kind of gastric juice the individual secretes. Subjects with a tendency to hyperacidity should avoid spicy and other foods which stimulate gastric secretion. On the other hand, low acidity calls for an entirely different diet. One cannot tell, except empirically, what foodstuffs are most suitable for any particular individual unless some sort of test is done. Many cases of heartburn have moderate or low gastric acidities, even achlorhydria, and the medicinal treatment is to be guided accordingly.

Summary

1. A series of 6679 test meals is analyzed according to age and other factors.

2. Age, next to constitutional predisposition, appears to be the dominating factor in gastric acidity. Thus the greatest incidence of high acidity occurs in the earlier age groups, while the low acid figures predominate in the later decades.

3. It is well known that certain diseases are associated with special ranges of acidity (e.g. duodenal ulcer with hyperacidity; pernicious anemia and cancer of the stomach with achlorhydria), but there is evidence to indicate that these acid levels precede the development of the disease, just as they persist after its cure.

4. It would appear that the degree of acidity—a constitutional factor—predisposes to a given disease, rather than that the disease produces a change in acidity.

5. It appears that the fifth decade constitutes the peak of functional activity as evidenced by the greater proportion of high acidities, while diminishing gastric acidities may be considered as evidence of aging, analogous to presbyopia, hypertension, arteriosclerosis, and the menopause.

6. The presence of high acid values in old age may be considered as an index to longevity.

7. The determination of gastric acidity is of practical value as an index of predisposition to certain diseases and as a guide to important therapeutic procedures (diet, medication).

8. Evidence is presented that in older patients, under observation for comparatively long periods, there is a tendency to a diminution or loss of gastric acidity.

9. A table of average values of gastric acidity, arranged according to age and sex, is proposed instead of the more arbitrary standards now in use.

We wish to express our appreciation of the collaboration of Dr. Harry Gauss, now of Denver, Colo., in preparing some of the earlier statistical material for this paper.

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COEXISTENCE OF PERNICIOUS ANEMIA AND LESIONS OF THE GASTROINTESTINAL TRACT*

I. CARCINOMA OF THE STOMACH

Consideration of Twenty Cases: Eleven Reported

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Review of Literature

Quincke,[1] in 1876, first mentioned the coexistence of carcinoma of the stomach and progressive pernicious anemia. Since that time, various cases in which there was coexistence of the two diseases have been reported.

It has long been difficult to distinguish certain cases of carcinoma of the stomach from pernicious anemia, since weakness, anorexia, gastric symptoms, insidious onset, and anemia are common to both conditions. The not uncommon absence of gastric symptoms and the occasional yellowish pallor in carcinoma, the not very uncommon severe loss of weight in pernicious anemia, and the occasional red bone marrow due to metastasis in carcinoma, serve to confuse the picture. Probably the two most important clinical characteristics that distinguish pernicious anemia from carcinoma of the stomach are sore tongue, and paresthesia and neurologic symptoms that suggest subacute combined degeneration of the posterior and lateral columns of the spinal cord. Diarrhea occurs much more commonly in pernicious anemia than in carcinoma.

The anemia of carcinoma of the stomach usually is of the hypochromic secondary type, but occasionally it is hyperchromic, such as that of pernicious anemia. Macrocytosis and high hemoglobin index and volume index strongly indicate pernicious anemia, although they are not absolutely diagnostic. Usually leukopenia is present in pernicious anemia, and ordinarily leukocytosis is present in carcinoma of the stomach. The usual relative lymphocytosis and the shift to the right of the polymorphonuclear leukocytes in pernicious anemia, and the presence of the so-called neutrophil of pernicious anemia are of considerable value in the diagnosis. Achlorhydria, present in practically every case of pernicious anemia, is found in only 50

* Submitted for publication November 29, 1932. From The Mayo Clinic, Rochester, Minnesota.

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or 60 per cent of cases of carcinoma of the stomach. To confuse the picture, myelocytes may occur in some cases in which carcinoma has invaded the bone marrow, and they may be present in some severe cases of pernicious anemia.

When the best criteria for distinguishing the two diseases are applied, there remain a few cases in which they are apparently coexistent. A number of cases has been reported, particularly in recent years. Some of these seem only to be cases in which the blood picture resembling pernicious anemia accompanies carcinoma of the stomach. In other cases apparently, the two diseases actually coexist, or there has been a consecutive development of the two.

One must distinguish between true cryptogenetic pernicious anemia and the blood picture resembling pernicious anemia, which may be so closely simulated at times by other diseases, particularly by sprue, and, as we have mentioned, occasionally by carcinoma. A perfect picture of pernicious anemia is represented by glossitis, paresthesia, and other evidences of degeneration of the spinal cord, diarrhea, little if any loss of weight, lemon yellow skin, increased hemoglobin index, increased volume index, marked general macrocytosis, leukopenia, relative lymphocytosis, presence of the "polymorphonuclear leukocyte of pernicious anemia," shift to the right of the neutrophils, decrease in platelets, increase in serum bilirubin, presence of urobilin and urobilinogen in the urine and their increase in the stool or duodenal contents, achlorhydria, response to treatment with liver or to the ingestion of gastric tissue, and the occurrence of remissions. One or more of these features may be lacking and still a diagnosis of true pernicious anemia may be entirely tenable. If most of these features are present in an individual case and carcinoma of the stomach is demonstrated either by roentgen-rays, by operation, or by necropsy, the two diseases will usually coexist.

There are several hypotheses as to the coexistence of these diseases. Most observers maintain that pernicious anemia and carcinoma coexist accidentally.[2, 3, 4, 5, 6, 7, 8, 9, 10] Fischer-Defoy and Lubarsch [11] think the coexistence accidental in some instances, and Naegeli,[12] and Bloch [13] believe this the usual explanation. Other observers believe that the blood picture of pernicious anemia may occur as a result of carcinoma of the stomach.[14, 15, 16, 17, 18] Fischer-Defoy and Lubarsch, Lazarus,[19] and Brandes [20] believe this is true in some instances. Some of this latter group of observers believe that actual pernicious anemia develops as a result of carcinoma of the stomach; others that only the blood picture of pernicious anemia occurs and that true pernicious anemia does not result from carcinoma of the stomach. Among the latter are Fischer-Defoy and Lubarsch, Pappenheim, and Zadek. Naegeli, Bloch, and Minot [21] believe it possible that the carcinoma develops on soil of pernicious anemia. Brandes, and Lazarus thought this the explanation in some cases.

It would be of great interest and value to determine whether pernicious

anemia is much more common among patients with carcinoma of the stomach than among other patients of the same sex and age, or whether carcinoma of the stomach is more common among those who have pernicious anemia than among others. If these points could be determined accurately in a large series of cases, one might learn whether pernicious anemia predisposes to carcinoma of the stomach, or vice versa.

Dunn [22] is of the belief, however, that this question cannot be settled in a clinic such as ours, in which the sampling of patients from distant communities is unequal.

Formerly, any form of hyperchromic macrocytic anemia, associated with leukopenia and with relative lymphocytosis, usually was assumed to represent pernicious anemia. However, at present, in addition to the blood picture, the absence of free hydrochloric acid is usually required, and the addition of one or more of the following symptoms is desirable: sore tongue, paresthesia, and diarrhea. In recent years, a great deal of attention has been paid to the character of the polymorphonuclear leukocytes.

Heinrichsdorff in 1912 made a critical review of all cases of the coexistence of the two diseases reported up to that time, and accepted only a few as unquestionable.

Although we shall not attempt to review in detail the previously reported cases it would appear that some of these cases, particularly those recently reported, have had all of the essential diagnostic features of pernicious anemia and carcinoma of the stomach, and, moreover, some of the patients have responded well to treatment with liver, liver extract, and desiccated swine stomach.

A few cases recently reported are those of Waterfield,[23] Cabot,[24] Castle,[25] Giffin and Bowler,[26] Neuburger,[27] Plummer and Simpson,[28] Simpson,[29] Sonnenfeld, Weinberg,[30] and Zadek (two cases). Strandell,[31] in a recent review of 117 cases of pernicious anemia, reported four cases associated with carcinoma of the stomach; Levine and Ladd [32] reported one case in 150 cases of pernicious anemia; Panton, Maitland-Jones and Riddoch,[33] none in 117 cases, and Rohner,[34] one in 127 cases.

Eisen,[35] in a group of 187 cases of carcinoma of the gastrointestinal tract, did not find a case of pernicious anemia, but in 20 of the 79 cases of carcinoma of the stomach the hemoglobin index was 1 to 1.5. Brandes, in a series of 66 cases of pernicious anemia observed from 1911 to 1919, found carcinoma of the stomach in four of 22 cases in which necropsy had been performed.

Neuburger is of the belief that there is an increased incidence of pernicious anemia in families in which carcinoma exists, and von Hoffmann [36] holds the same view. Cornell [37] thinks that carcinoma of the stomach not infrequently complicates an already existing pernicious anemia. Davidson and Gulland [38] (three cases), Hurst,[39] Naegeli (" very few "), and Ungley [40] have seen the occurrence of the two conditions together.

Data from The Mayo Clinic

Records of cases from 1925 to 1930, in which pernicious anemia was positively diagnosed or was considered possible, were taken from the files. These records were examined to find in how many cases carcinoma of the stomach was positively diagnosed or was considered possible. All of the records in which both diagnoses had been made or suggested were critically examined to determine in how many both diagnoses were certainly or almost certainly established. Eight records were found which met this requirement.

For the purpose of determining the percentage of cases in which carcinoma of the stomach afflicted patients with pernicious anemia, a smaller subgroup of records was taken. That is, all records from 1928 to 1930, in which pernicious anemia was positively diagnosed or was considered possible were taken from the preceding, larger group. There were 784 of these. The method of examination of the records of this subgroup was considerably more exact and laborious. At the very outset the entire 784 records were critically examined to determine the number in which the diagnosis of pernicious anemia was well established, and in 658, it was found to be certainly or probably established. Of these 658 cases there were four (0.6 per cent) in which the diagnosis of carcinoma of the stomach was established. This figure may differ greatly from that given in other clinics, for reasons stated elsewhere.

Three other cases in which the two diseases coexisted have been added; these occurred in 1931 and 1932 and before 1925. During this same period there were four more cases in which the coexistence of the two diseases was somewhat doubtful. In all four the existence of pernicious anemia was practically certain, but in two the degree of malignancy (of polyps) was only graded 1 [41]; in one case the diagnosis of malignant polyps (inoperable) was made only by the roentgenologist, and in the fourth case though roentgenograms indicated carcinoma, at a later date another roentgenologic examination elsewhere was reported negative.

Thus, there were 15 cases in which carcinoma of the stomach and pernicious anemia coexisted with more or less certainty. There also were three cases of definitely diagnosed carcinoma, possibly accompanied by pernicious anemia, and one case of malignant polyp possibly accompanied by pernicious anemia. In still another case in which operation was performed at the clinic for carcinoma of the stomach, it is reported four years after operation that the blood now shows most of the characteristics of pernicious anemia except shift of the polymorphonuclear leukocytes to the right, and that the patient has responded to treatment by liver.

In most instances, the diagnosis of pernicious anemia was made by a physician in the Section on Hematology. A definite diagnosis of pernicious anemia is based on the existence of most, if not all, of the significant features of history, general examination, and known laboratory tests, and a

probable diagnosis on the existence of many of these features but the lack of some of the important ones. A definite diagnosis of carcinoma of the stomach is based on demonstration of the disease at operation or necropsy, with or without positive roentgen-ray observations, and a probable diagnosis is based on a positive report by the roentgenologist. It is possible that some cases of pernicious anemia have been overlooked when the diagnosis was frankly carcinoma of the stomach, because an extensive study for pernicious anemia usually was not made in such cases. It seems likely, however, that almost all instances of carcinoma in cases of frank pernicious anemia were discovered, since roentgenologic examination of the stomach is made as a routine in almost all cases of pernicious anemia as a precautionary measure. It is likely that many cases of carcinoma of the stomach were formerly overlooked when roentgen-rays were not used as a routine procedure when the diagnosis of pernicious anemia was evident. A search for carcinoma should be made in cases of pernicious anemia, especially when the patient has lost much weight.

In this paper are included only the 11 cases in which there was definite or probable carcinoma of the stomach in association with definite or probable pernicious anemia. They are reported in the order of importance as examples, rather than chronologically. In six of these cases the sequence of the two diseases as to incidence could not be established. In three the carcinoma seemed to follow the pernicious anemia (by seven years, one and a half years, and seven to eight years). In one case, pernicious anemia was diagnosed 32 months after partial resection of the stomach for carcinoma, although there was some suggestion of pernicious anemia ten months after operation. In another case, pernicious anemia was diagnosed six years after a similar operation, but there was considerable suggestion of its presence before operation.

The series therefore yielded no definite indications as to a fixed sequence of development. The fact that in three cases carcinoma seemed to follow the development of pernicious anemia, and in two cases pernicious anemia apparently followed the development of carcinoma suggests that each disease may possibly predispose to the other. On this basis the apparently simultaneous occurrence of both in six of the cases might not be a matter of mere chance. In any event, the two diseases do not appear to be antagonistic.

When both diseases are present, each disease should be treated as though the other did not exist. Resection of the stomach for carcinoma should not be denied to a patient simply because he also has pernicious anemia, nor should the treatment of pernicious anemia be neglected because of the seriousness of the illness due to carcinoma. The diseases seem to affect each other's progress very little. It seems best, however, to institute radical treatment for pernicious anemia before operation so that neurologic lesions may be prevented and the patient be placed in the best possible condition for operation.

Pernicious Anemia and Carcinoma of the Stomach Apparently Developing Almost Simultaneously (Cases 1 to 6)

*Case I.** A farmer, aged forty-four years, from Colombia, South America, registered January 30, 1932. His mother had died of carcinoma of the stomach, one brother had died of tuberculosis, and a sister of typhus fever. The patient had had influenza in 1919, gonorrhea in 1920, and malaria in 1922. His chief complaints were recurring weakness, epigastric pain, and diarrhea for eighteen months. He noted that his tongue had been red and sore for the last eight months, and that mild numbness had been present in the fingers for the last year. His physician had found that anemia was present, and had prescribed a small amount of liver extract.

The blood pressure, pulse rate, and temperature were normal. The tongue was slightly red and somewhat smooth. The concentration of hemoglobin was 10.2 gm. in each 100 c.c. of blood. The volume index was 1.35. Erythrocytes numbered 2,140,000 and leukocytes 4,600 in each cubic millimeter of blood. In morphologic examination of the blood the following features were noted: normal differential leukocyte count; moderate anisocytosis; slight polychromatophilia; reticulated erythrocytes 1.5 per cent; macrocytosis without poikilocytosis or stippling; hyperchromasia of individual erythrocytes; and neutrophils designated as of toxic type (grade 2) with large fat lobes, a picture probably not characteristic of pernicious anemia. Urinalysis and serologic test for syphilis were negative. Achlorhydria was found to be complete by the fractional method of analysis. The concentration of bilirubin was 1.7 mg. in each 100 c.c. of serum, and the van den Bergh reaction was indirect. The concentration of calcium was 9.6 mg. in each 100 c.c. of serum. Parasites and ova were absent in three specimens of stool. A roentgenogram of the thorax gave negative results and one of the stomach revealed carcinoma involving the lesser curvature of the middle and upper third. The patient was given 20 c.c. of a preparation of liver extract intravenously. Four days later the reticulated erythrocytes had risen from 3 to 21.8 per cent.

At operation an extensive polypoid carcinoma of the stomach, with extensive involvement of the lymph nodes was found. The growth was incompletely removed. Recovery was uneventful. In a letter received from a brother, it was stated that the patient died five months after the exploratory operation.

The history of sore tongue, diarrhea, numbness, high hemoglobin index and volume index, and macrocytosis favored a diagnosis of pernicious anemia, but the blood picture was not entirely characteristic, principally because of the character of the leukocytes. Taking into account the patient's residence in the tropics and the presence of macrocytosis, sore tongue, and diarrhea, sprue also was considered. The rapid response of the reticulated erythrocytes following injection of liver extract made the diagnosis of pernicious anemia or sprue (probably pernicious anemia) practically definite. The presence of carcinoma was proved at operation.

Case II. A church sexton, aged fifty-seven years, registered May 24, 1930. He complained of weakness, vague epigastric distress, fatiguability, palpitation and tachycardia on exertion, anorexia, occasional gaseous dyspepsia, and some burning in the epigastrium which was relieved by ingestion of food. He had lost 15 to 20 pounds in weight. He complained of insomnia, worrying and depression. Vomiting, hematemesis, melena, soreness of mouth or tongue, paresthesia of the extremities, and diarrhea, were not present.

The patient was markedly pale with sallow complexion; he was emaciated and weak. Definite atrophy of the papillae was observed on the edge of the tongue. There was a systolic murmur over the cardiac area. The neurologic examination was

* Unimportant data usually are omitted in reports of cases.

negative. The concentration of hemoglobin was 6.8 gm.; erythrocytes numbered 1,100,000, and leukocytes 6,300. The color index was 1.85; the percentages of the various types of leukocytes were as follows: lymphocytes 21.5, monocytes 0.5, transitionals 4, neutrophils 71.5, and eosinophils 2.5. The percentage of reticulated erythrocytes was 1.7. The blood smear was characteristic of pernicious anemia. Achlorhydria was noted following fractional analysis of a test meal. Blood, graded 2, was found in the contents of the stomach. A roentgenogram revealed a pedunculated tumor in the median portion of the stomach, which was considered probably malignant and the advisability of operation was thought questionable. The diagnosis was pernicious anemia and pedunculated tumor of the stomach.

At operation, a polypoid tumor, about 6 cm. in diameter, and adjacent nodes were removed. The pathologist reported adenocarcinoma, graded 2, with involvement of lymph nodes.

Following the administration of liver extract there was a typical response in reticulated erythrocytes which reached a peak of 11.1 per cent. When the patient was dismissed, the concentration of hemoglobin was 58 per cent (Dare); erythrocytes numbered 2,780,000, and leukocytes 6,000. Four months later, the concentration of hemoglobin was 66 per cent; erythrocytes numbered 4,270,000, and leukocytes 5,400; the differential count was normal. The percentage of reticulated erythrocytes was 0.8. Definite features of pernicious anemia were observed in blood smears, including macrocytosis and a shift to the right in the leukocyte picture. The patient made an excellent recovery.

Atrophy of the tongue, high hemoglobin index, blood smear characteristic of pernicious anemia, make the presence of pernicious anemia practically definite. The presence of carcinoma was proved at operation.

Case III. A concrete worker, aged fifty-six years, registered at the Clinic August 3, 1926. One brother had died of carcinoma. Three months before admission, the patient became weak, lost his appetite, and 23 pounds in weight. Mild attacks of belching, a bad taste in the mouth, edema of the ankles, nervousness, worry, and insomnia were present. The tongue was not sore and neither diarrhea nor paresthesia was present.

The patient was markedly pale, with a lemon yellow tint to the skin and conjunctivae. He was moderately emaciated and weak. Atrophy of the tongue and dental sepsis were present. There was a faint systolic murmur over the cardiac area. Evidence was found of a mild peripheral neuritis such as is seen in early involvement of the nerves in pernicious anemia. The concentration of hemoglobin was 41 per cent (Dare); erythrocytes numbered 1,830,000 and leukocytes, 8,700. The color index was 1.1+. The percentages of the various types of leukocytes were as follows: lymphocytes 35, monocytes 1, transitionals 1, neutrophils 62, and eosinophils 1. The morphologic examination revealed moderate anisocytosis and polychromatophilia, and slight poikilocytosis and basophilic stippling. The concentration of bilirubin was 5 mg. in each 100 c.c. of serum; the van den Bergh reaction was direct. Achlorhydria was found by the fractional method of analysis. Blood (graded 2) was found in the gastric contents. Roentgenologic examination gave negative results. The diagnosis was pernicious anemia with mild peripheral neuritis.

The patient was given three transfusions of blood and died in a severe reaction after the third transfusion.

Necropsy revealed the typical changes of pernicious anemia, red bone marrow, hemosiderosis of the liver, fatty changes of the myocardium and slight splenomegaly (264 gm.). A carcinoma 4 by 5 cm. and a small ulcer on the anterior wall of the stomach were found, with metastasis to the regional lymph nodes and omentum. There were several acute ulcers of the mucosa of the transverse colon.

Lemon yellow skin and sclerae, atrophy of the tongue, peripheral neuritis, high color index, necropsy findings of pernicious anemia, including enlarged spleen, make

the presence of pernicious anemia almost certain. Treatment with liver was not then in use. Carcinoma was found at necropsy.

Case IV. A carpenter, aged fifty-nine years, registered May 4, 1929. He had had an incision of a perianal abscess ten years previously. He had been weak, pale, and nervous since. Constipation had been present for five years, and anorexia for two and a half years, following an attack of bronchitis. Roentgenograms of the stomach had twice given negative results. Eighteen months prior to registration the erythrocyte count was 1,000,000. He had been given liver, and liver extract and a transfusion of blood and had improved temporarily. For the last year there had been a cotton-like sensation in the soles of his feet, but neither soreness of the tongue nor diarrhea had been noted. During the last six months his condition had grown definitely worse.

The patient was yellowish pale, markedly weak, and prematurely senile. A generalized coarse tremor and evidence of subacute, combined degeneration of the posterior and lateral columns of the spinal cord were present. The concentration of hemoglobin was 51 per cent; the erythrocytes numbered 2,700,000 and the leukocytes 7,500. The color index was 0.9 +. The percentages of the various types of leukocytes were as follows: lymphocytes 30, monocytes 1, transitionals 1.5, neutrophils 62.5, eosinophils 4, and basophils 1. The percentage of reticulated erythrocytes was 0.9. The blood smear was characteristic of pernicious anemia. The presence of achlorhydria was proved by the histamine method. There was a moderate amount of fresh blood in the gastric contents. Roentgenograms revealed the presence of a polypoid tumor on the posterior wall of the middle third of the stomach, whether malignant or benign could not be determined, and partial destruction of the third rib on the right side, suggestive of osteitis fibrosa cystica. The diagnosis was pernicious anemia with combined sclerosis of the spinal cord, polypoid tumor of the stomach, and questionable metastasis to the third rib.

At operation, a pedunculated papillary tumor about 4 cm. in diameter was excised from the posterior wall of the stomach, also a small nodule 2.5 cm. distant from the main mass. The pathologist reported that the polyp (2.5 by 0.5 cm.) and the nodule (1 cm.) were adenocarcinomatous, both graded 2 +. Following operation, the patient went into shock. Solutions of acacia and of glucose were given intravenously, blood transfusion was carried out, and the oxygen tent was used, all without success. Permission for necropsy was refused.

The yellowish pallor, remission of symptoms after liver extract, blood smear picture, paresthesia, combined degeneration of the posterior and lateral columns of the spinal cord, supported the diagnosis of pernicious anemia. The presence of carcinoma was proved at operation.

Case V. A farmer, aged sixty-six years, registered February 27, 1930. His family history was essentially negative. He complained of an infected toe, of dizziness, and of buzzing in the left ear. Slight irregularity in the bowel movements had been noted but diarrhea, bloody or tarry stools had not been observed. The concentration of hemoglobin was 15.2 gm. and the erythrocytes numbered 3,700,000. The patient returned September 10, 1931, because of loss of weight, sore tongue, anorexia, and tingling and swelling of the feet.

The blood pressure, pulse rate, and temperature were normal. The patient was emaciated. The tongue was smooth. The thorax and abdomen were normal. The concentration of hemoglobin was 9.7 gm.; erythrocytes numbered 2,350,000 and leukocytes 10,700 in each cubic millimeter of blood. A blood smear was characteristic of pernicious anemia. Basophilic stippling, and an occasional Howell-Jolly body were observed. The differential count was normal. Neutrophils were of the toxic type, graded 3. The percentage of reticulated erythrocytes was 1.7. Achlorhydria was found by fractional analysis of a test meal. The urinalysis was negative. A roent-

genogram revealed the presence of a large, hard intragastric tumor at the pyloric end of the stomach, and a normal thorax.

Partial gastrectomy was performed; a polypoid carcinoma about 6 cm. in diameter was found involving the antrum: The patient made a good recovery and was given from 2 to 6 vials of liver extract daily, and one transfusion of blood. Unfortunately, estimation of reticulated erythrocytes was not made often enough to determine their course. When the patient was dismissed the concentration of hemoglobin was 52 per cent; erythrocytes numbered 2,480,000 and leukocytes, 5,300.

A letter from the patient's widow stated that he died two and a half months after the operation. For a month after operation he took one-half pound of liver daily.

The achlorhydria, the blood picture, history of sore tongue, and appearance of tongue at the time of examination, indicated pernicious anemia. Operation established the diagnosis of carcinoma of the stomach. It seems unlikely that the characteristic blood picture and sore tongue were due to carcinoma of the stomach. The patient probably died as a result of carcinoma, although his failure to take liver during the last six weeks of his life suggests that pernicious anemia may have been a contributing cause.

Case VI. A laborer, aged sixty-one years, registered June 30, 1930. During the previous year he had been weak, and fatigued, with indefinite sore tongue; following treatment for anemia with liver extract he improved temporarily. For the last two months, dyspnea on exertion, increasing constipation, gaseous distention, and dull pain in the abdomen had occurred. Neither nausea, vomiting, diarrhea, nor paresthesia had been present, but the tongue was sore at the time of admission.

The patient was pale. The abdomen was distended. Ascites, an ulcerative process about the umbilicus, and an irregular mass in the upper part of the abdomen were observed. The concentration of hemoglobin was 7.9 gm.; erythrocytes numbered 1,600,000, and leukocytes 9,900 in each cubic millimeter of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 23.5, monocytes 1.5, transitionals 2.5, neutrophils 70.5, and eosinophils 2.5. A blood smear was characteristic of pernicious anemia. Achlorhydria was found following fractional analysis of a test meal. There was no blood in the gastric contents. Roentgenograms revealed the presence of a carcinoma of the lower third of the stomach and bilateral infiltration of the lungs, considered metastatic. The diagnosis was pernicious anemia and carcinoma of the stomach with metastasis to the lungs. The patient returned home and died three weeks later. Necropsy was not performed.

High index of hemoglobin, sore tongue, characteristic blood smear picture, and response to liver extract supported a diagnosis of pernicious anemia. Carcinoma of the stomach was practically proved by the mass in the abdomen, and by roentgenograms of stomach and lungs.

Pernicious Anemia Apparently Following Carcinoma of the Stomach (Cases 7 and 8)

Case VII. A housewife, aged forty-seven years, registered September 4, 1920, complaining of stomach trouble and weakness. Her mother had died of carcinoma of the breast. The patient had had diarrhea since childhood. For ten years, periodic indigestion, pain in the abdomen two or three hours after meals, nausea with suggestive relief from soda, and pain in the abdomen at night had been present. Six or seven months previously the Sippy diet had given relief. A short time before admission, the symptoms returned and she vomited fresh blood. There had been intermittent soreness of the tongue but no paresthesia.

The patient was well nourished, with moderate pallor and weakness. A mass was present in the upper left side of the abdomen. Stomatitis and glossitis were present. The concentration of hemoglobin was 40 per cent; erythrocytes numbered 3,200,000

and leukocytes 5,000. The color index was 0.6 +. The percentages of the various types of leukocytes were as follows: lymphocytes 32.5, neutrophils 63.5, eosinophils 3, and basophils 1. In morphologic study of the blood, the following features were noted: slight anisocytosis, poikilocytosis, and polychromatophilia. There was occult blood in the stools. Achlorhydria was found by the fractional method of analysis. There was no blood in the gastric contents. Carcinoma of stomach of questionable operability was revealed by roentgen-rays. The diagnosis was carcinoma of the stomach and secondary anemia.

At operation, a large, ulcerated, necrotic and very malodorous carcinoma was found on the posterior wall of the stomach above the incisura, completely encircling the stomach with extensive involvement of the omentum. Two-thirds of the stomach above the incisura was resected; 2.5 cm. of the pyloric end and the dome of the stomach were preserved. The pathologist reported carcinoma, 12 by 11 by 5 cm., without involvement of the lymph nodes. Treatment by irradiation was given several times during the next four years. The patient had attacks of diarrhea, soreness of the tongue, and transient numbness of the fingers, and one attack each of arthritis and cystitis; she was constantly pale and her weakness was gradually increasing.

When the patient was readmitted, November 24, 1926, examination revealed extreme weakness and pallor, ecchymoses under the tongue, a palpable spleen, questionable enlargement of the liver, and slight edema of the ankles. The concentration of hemoglobin was 31 per cent; erythrocytes numbered 1,440,000 and leukocytes 3,200. The color index was 1.0 +. The percentages of the various types of leukocytes were as follows: lymphocytes 42.5, monocytes 3.5, transitionals 1.5, neutrophils 51, eosinophils 1, and basophils 0.5. The volume index was 0.94. Morphologic study revealed moderate anisocytosis and poikilocytosis, and slight polychromatophilia and basophilic stippling. Achlorhydria was noted following analysis of a simple Ewald meal. There was no blood in the gastric contents. Roentgenograms revealed that carcinoma had not recurred and that there was no evidence of metastasis to the thorax or bones. A diagnosis of pernicious anemia was made.

Transfusions of blood and dilute hydrochloric acid and liver were given. At dismissal, the concentration of hemoglobin was 70 per cent; erythrocytes numbered 3,140,000 and leukocytes 6,600. The color index was 1.1 + and the volume index 1.13.

A letter from the patient three years later stated that she had improved, good health had been maintained, and blood counts were normal. Another letter was received five years later, but nothing was said regarding her health.

Diarrhea, soreness of tongue, stomatitis, glossitis, numbness of fingers, increased hemoglobin index late in the disease, response to treatment by liver (this patient also was given transfusions) indicated pernicious anemia. The presence of carcinoma of stomach was proved at operation. Definite evidence of pernicious anemia developed six years after removal of two-thirds of the stomach for carcinoma, although there was considerable suggestion of it in the stomatitis and glossitis before operation. Whether the operation was a factor in the development of the pernicious anemia must remain conjectural.

Case VIII. A housewife, aged fifty-three years, registered October 2, 1926, complaining of anemia and weakness. She had had symptoms typical of peptic ulcer with vomiting for the preceding twelve years. Eight years previously she had had "flu" and weakness and pallor afterward, with increase in weakness, fatiguability and dyspnea on exertion in the last year, but without loss of weight, soreness of mouth or tongue, diarrhea, or paresthesia. She had been treated with iron, raw beef, sunlight, and what she called serum.

The patient was markedly pale, with a lemon yellow tint. The tongue was normal. There was a mass in the mid-epigastrium. The concentration of hemoglobin was 27 per cent. Erythrocytes numbered 3,080,000 and leukocytes 4,800. The color index was 0.4 +. The percentages of the various types of leukocytes were as follows:

lymphocytes 33.5, transitionals 2, neutrophils 59, eosinophils 3, and basophils 1.5. Morphologic examination of the blood revealed moderate poikilocytosis and slight anisocytosis and polychromatophilia. Achlorhydria was observed in an analysis of a fractional test meal. There was a trace of blood in the gastric contents. A roentgenogram disclosed the presence of a tumor, considered benign, on the posterior wall of the middle third of the stomach. Diagnosis was benign tumor of the stomach and severe secondary anemia.

At operation, a pedunculated tumor, about 3 cm. in diameter, was excised. The pathologist reported a pedunculated adenoma containing an adenocarcinoma graded 2.

The patient returned ten months later for a check-up. She still tired easily, was free of gastric symptoms, but had intermittent tingling of hands and feet. Neither soreness of the mouth or tongue, nor diarrhea was present. The concentration of hemoglobin was 62 per cent; erythrocytes numbered 3,710,000 and leukocytes 7,700. The color index was 0.8+. The percentages of the various types of leukocytes were as follows: lymphocytes 29.5, monocytes 2, transitionals 3, neutrophils 59, eosinophils 4.5, and basophils 2. In morphologic studies of the blood the following were noted: slight anisocytosis, slight poikilocytosis, and slight polychromatophilia. Achlorhydria was found by the fractional method of analysis. There was no blood in the gastric contents. A roentgenogram of the stomach did not reveal recurrence. Dilute hydrochloric acid and a diet high in vitamins were prescribed.

Twenty-two months later the patient again returned because of increasing constant numbness of the feet and hands. Moderate pallor and evidence of definite subacute combined sclerosis of the spinal cord were noted. The concentration of hemoglobin was 68 per cent; erythrocytes numbered 2,070,000 and leukocytes 5,400. The color index was 1.2+. A blood smear picture was characteristic of pernicious anemia. Achlorhydria was found by the fractional method of analysis. After liver or liver extract and dilute hydrochloric acid had been taken for one month the concentration of hemoglobin was 58 per cent; erythrocytes numbered 3,190,000 and leukocytes 6,100. The color index was 0.9+, and there was slight lymphocytosis.

The patient returned June 11, 1931. She had not been taking liver extract regularly. The numbness and weakness had become worse. Examination revealed evidence of marked combined degeneration of the posterior and lateral columns of the spinal cord. The concentration of hemoglobin was 59 per cent; erythrocytes numbered 1,990,000 and leukocytes 5,900. The differential count was normal. A blood smear was characteristic of pernicious anemia. The patient was instructed to use 6 vials of liver extract No. 343 daily. The last report showed that the erythrocytes numbered 3,500,000 and the concentration of hemoglobin was 68 per cent.

The anemia was of the hypochromic secondary type before operation, but ten months after operation numbness and tingling were present and thirty-two months after operation there was a definite blood picture of pernicious anemia. Whether the pernicious anemia was developing before operation, coexistent with the gastric lesion, or whether it occurred as a result of partial gastrectomy cannot be determined, but the former hypothesis seems more plausible. Adenocarcinoma graded 2 was demonstrated at operation, but the fact that the patient was living five years after operation suggests that the lesion was only mildly malignant or that removal was absolutely complete.

Carcinoma of the Stomach Apparently Developing after Pernicious Anemia (Cases 9 to 11)

Case IX. A physician, aged fifty-three years, registered June 27, 1923. The family history was not significant. His chief complaint was of general weakness. He had had influenza in 1918, pulmonary tuberculosis in 1919, and malaria in 1921.

Following this his skin became yellow and anemia developed with a concentration of hemoglobin of 43 per cent and erythrocytes numbering 1,700,000. The tongue had been a little sore. The erythrocyte count increased to 4,000,000 in 1922, but in March, 1923, loss of weight, discomfort in the stomach and bowels, nausea and anorexia developed.

At examination the skin had a lemon tint. The concentration of hemoglobin was 47 per cent; erythrocytes numbered 1,850,000, and leukocytes 3,600. The color index was 1.2. The differential count was normal. In morphologic study of the blood the following features were noted: moderate anisocytosis, slight poikilocytosis, basophilic stippling, and polychromatophilia. The percentage of reticulated erythrocytes was 2.4. Achlorhydria was found by the fractional test of an Ewald meal. The Wassermann reaction was negative. Urinalysis was negative except for a slight trace of urobilin and urobilinogen. Malarial parasites were absent. Roentgenograms revealed the presence of an old lesion in the apex of the right lung and of a normal stomach and gall-bladder. Following the use of hydrochloric acid and Fowler's solution, drainage of the duodenum, flushing of the bowel, and two transfusions of blood, the concentration of hemoglobin rose to 77 per cent and the erythrocyte count to 4,280,000.

In April, 1924, palpitation, dyspnea, slight edema of the ankles, constipation, considerable soreness at the right costal margin, occasional sore tongue, and slight numbness and tingling in the hands and feet occurred. At examination June 17 the tongue was smooth, and the color lemon yellow. The concentration of hemoglobin was 35 per cent; erythrocytes numbered 1,370,000, and leukocytes 2,400. The color index was 1.2. Occasional normoblasts were noted. The differential count was essentially normal. Morphologic studies revealed moderate anisocytosis and slight poikilocytosis and polychromatophilia. Achlorhydria was found by the fractional method of analysis. Transfusions, Fowler's solution, and hydrochloric acid were given. Following treatment the concentration of hemoglobin was 73 per cent; erythrocytes numbered 3,070,000 and leukocytes 3,400.

The patient returned July 14, 1925. He had become easily fatigued, but neither sore tongue nor diarrhea had developed. The paresthesia had disappeared. Soreness in the region of the gall-bladder was still present. Moderate pallor was noted. Prostatitis (graded 2) was found. The blood pressure, pulse rate and temperature were normal. The concentration of hemoglobin was 44 per cent; erythrocytes numbered 2,480,000, and leukocytes 5,100. Morphologic studies showed the presence of moderate anisocytosis and poikilocytosis, and slight basophilic stippling and polychromatophilia. The differential count was normal except for the presence of 7.5 per cent of eosinophils. A roentgenogram did not reveal the gall-bladder. Hepatic function, serum bilirubin, and concentration of blood urea were normal. The prostatitis was treated and the tonsils were removed.

The patient returned July 12, 1926. He had felt well until a month previous when nausea and a distaste for food suddenly developed. He had had an occasional attack of pain in the right subcostal region with distention, belching and heartburn, for which he had had the gall-bladder drained. He also had had an attack of precordial and substernal pain radiating down the left arm. Except for pallor and absent knee and ankle reflexes, general examination gave essentially negative results. The concentration of hemoglobin was 25 per cent; erythrocytes numbered 1,100,000 and leukocytes 4,650. The hemoglobin index was 1.1. Transfusions, hydrochloric acid, Fowler's solution, and a few doses of gentian violet by mouth were given. Following treatment the concentration of hemoglobin was 42 per cent and the erythrocyte count was 2,890,000.

The patient again returned, September 1, 1930. He had been taking liver during the previous four years and had been doing well, working every day, and had had no characteristic symptoms. General examination was essentially negative. The con-

centration of hemoglobin was 15.2 gm.; erythrocytes numbered 4,110,000 and leukocytes 3,700. Lymphocytosis was relatively marked, and macrocytosis was definite, but there was no right shift in the polymorphonuclear leukocytes. A test meal showed fresh blood in the stomach. A roentgenogram of the stomach was negative. It was advised that another roentgenogram of the stomach should be made at an early date.

The patient returned July 10, 1931. Two months after his previous return home he had taken a test meal which revealed blood, and had had a roentgenogram made of the stomach, which had been pronounced negative. In February 1931, following influenza, the concentration of hemoglobin had been 29 per cent and the erythrocytes had numbered 2,000,000. In May 1931, he had vomited blood, and a roentgenogram had indicated an obstruction in the esophagus. There had been a little difficulty in swallowing. An increased amount of liver, liver extract, and ventriculin improved the condition of the blood, but loss of weight continued.

General examination was negative except for the pallor. The concentration of hemoglobin was 9 gm.; erythrocytes numbered 3,540,000 and leukocytes 5,700. Morphologic studies revealed the following: slight poikilocytosis, anisocytosis, and polychromatophilia. Platelets numbered 184,000 and reticulated erythrocytes 1.4 per cent. There was little evidence of pernicious anemia in blood smears. Polymorphonuclear leukocytes were of the toxic type, graded 1 to 2. The serologic test for syphilis was negative. Complete achlorhydria was proved by a fractional analysis of a test meal; a trace of blood in the gastric contents and occult blood in the stools were noted. A roentgenogram revealed the presence of a carcinoma involving the lower end of the esophagus and the cardiac end of the stomach. After surgical consultation, the patient was advised not to undergo operation. He was told that dilatation or gastrostomy might be necessary if the esophagus became completely obstructed.

Yellowish pallor, sore tongue, frequent remissions and relapses, moderately high hemoglobin index, urobilin and urobilinogen in urine, numbness and tingling, macrocytosis, improvement following the liver extract and ventriculin make the diagnosis of pernicious anemia almost positive. The presence of a carcinoma in the stomach was revealed by repeated blood in the gastric contents and stools, and by roentgenograms, seven to eight years after the apparent onset of pernicious anemia.

Case X. A real estate agent, aged fifty-six years, registered August 19, 1919. One brother had died of carcinoma of the stomach. The patient had lost 30 pounds in weight; he was pale, sore in various parts of the abdomen, and had attacks of weakness.

At examination marked pallor was noted. The spleen was palpable. The concentration of hemoglobin was 49 per cent; erythrocytes numbered 2,240,000 and leukocytes 4,200. The color index was 1.1. The differential count was normal. Morphologic study revealed moderate anisocytosis and poikilocytosis. Achlorhydria was observed following fractional analysis of a simple Ewald meal. Two roentgenograms of the stomach gave negative results. The diagnosis was probable pernicious anemia. Anemia progressed rapidly and a few days later the concentration of hemoglobin was 40 per cent; erythrocytes numbered 1,590,000, and the color index was 1.2 +. Improvement occurred following two transfusions of blood, and the taking of Fowler's solution and Blaud's pills.

The patient returned to the Clinic March 16, 1923. Six months before, numbness and tingling had occurred in the hands and feet, and the anemia had recurred. There were a few cracks in the tongue and moderate pallor. The concentration of hemoglobin was 64 per cent; erythrocytes numbered 2,480,000 and leukocytes 4,400. He was given two transfusions of blood, dilute hydrochloric acid, Fowler's solution, and Blaud's pills.

The patient again came to the Clinic three and a half years later because of anemia, a "load on his stomach," anorexia, weakness and some numbness in hands and feet. No soreness of the tongue or diarrhea had been noted.

Examination revealed loss of strength (graded 2), xerotic skin and an irregular mass in the left portion of the epigastrium. The concentration of hemoglobin was 75 per cent; erythrocytes numbered 4,390,000 and leukocytes 10,500. The differential count was normal. A roentgenogram of the stomach revealed carcinoma of the pyloric end, with fairly marked obstruction, probably operable. The diagnosis was carcinoma of the stomach, and pernicious anemia with peripheral neuritis.

At operation a perforating type of carcinoma of the pyloric end of the stomach, with extensive implants in the gastrocolic omentum and several small nodules in the liver were discovered. Posterior gastroenterostomy was done. Twelve days after operation, gastric retention, gradual failure, and coma led to death. Necropsy revealed carcinoma of the pyloric end of the stomach with metastasis to the peritoneum, regional lymph nodes, pancreas and liver; multiple polypi of the stomach; generalized peritonitis and septic splenomegaly.

A high hemoglobin index, remission, paresthesia, peripheral neuritis, and the condition of the tongue make a diagnosis of pernicious anemia almost positive. Carcinoma was found at operation. Evidence of carcinoma did not appear until seven and a half years after the discovery of pernicious anemia.

*Case XI.** A farmer, aged fifty-two years, registered May 5, 1915. About a year previously hemorrhoidectomy had been performed because of mucus and blood in the stools. Cramps in the lower part of the abdomen, gas, nausea, vomiting, constipation, bloody and watery stools, and bearing down in the rectum soon developed, and the patient's appetite became poor.

At examination the patient was pale. Edema was absent. There was a systolic murmur at the apex. External hemorrhoids (graded 2) were found. The concentration of hemoglobin was 30 per cent; erythrocytes numbered 1,300,000 and leukocytes 4,700. The color index was 1.1. The percentages of the various types of leukocytes were as follows: polymorphonuclears 53, lymphocytes 39.3, eosinophils 7, basophils 0.3 and neutrophilic myelocytes 0.3. Morphologic studies revealed marked anisocytosis, and slight poikilocytosis, granular degeneration, and polychromatophilia. *Endamebae histolyticae* were discovered in the stools. Urinalysis, Wassermann reaction of the blood, and proctoscopic examination were negative. Pernicious anemia, and infection with amebae were diagnosed, and arsenic, iron, emetin, and enemas of coal oil were given.

The patient returned November 15, 1916, with improvement in strength and color. Numbness in the fingers, and weakness had developed. There was a rectal discharge of mucus. Pain in the abdomen had been general. Severe diarrhea had developed, with fresh blood in the stool. There was a gnawing sensation in the epigastrium which was relieved by the ingestion of food. Nocturia, anorexia, sore mouth, dry and "beefy" tongue, and loss of weight were present.

The blood pressure was 92 systolic and 50 diastolic in millimeters of mercury. The pulse rate was 88 beats each minute. A round mass approximately 3 cm. in diameter was present just below the left costal margin, which moved with respiration. The liver edge was palpable 5 cm. below the costal margin. The spleen was palpable, and the right lower part of the thorax was tender. Hemorrhoids (graded 2), albumin (graded 2), and hyaline casts (graded 2) were present. There was an occasional pus cell in the urine. Achlorhydria was observed following fractional analysis of an Ewald meal. The concentration of hemoglobin was 60 per cent; erythrocytes numbered 2,850,000 and leukocytes 9,500. The differential count was normal except for 10 per cent of eosinophils. A roëntgenogram revealed the presence of an inoperable carcinoma of the stomach. Neurologic examination indicated involvement of the posterior columns of the spinal cord. Diagnosis was inoperable carcinoma of the stomach with pernicious anemia. The patient died November 22, 1922 at his home. Necropsy was not performed.

* Reported by Giffin and Bowler.

The history of diarrhea, soreness of mouth, beefy red tongue with anemia, high index of hemoglobin, and evidence of neurologic involvement make the diagnosis of pernicious anemia practically certain. A roentgenogram of the stomach gave definite evidence of carcinoma. Operation and necropsy were not performed. Evidence of carcinoma did not appear until one and a half years after the appearance of pernicious anemia.

SUMMARY

Carcinoma of the stomach and pernicious anemia may coexist. Either disease may occur first, but in most instances their occurrence appeared to be simultaneous, and a definite sequence was not established in this study.

In 11 cases, the coexistence was certain or almost certain, and these cases are reported. In four the coexistence was somewhat doubtful; and in five other cases the occurrence of both diseases together was possible.

Each disease should be treated as if it existed alone. The specific treatment for pernicious anemia should be instituted before operation for carcinoma, in order to avoid serious consequences from the anemia, and to forestall if possible neurologic complications.

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RENAL INSUFFICIENCY FOLLOWING BLOOD TRANSFUSION—RECOVERY AFTER VENESECTION*

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In 1931, Bordley[1] reviewed the literature and analyzed 17 cases of renal insufficiency following blood transfusions. Eleven of these 17 cases died and six recovered. No patient recovered who had received more than 540 c.c. of blood; none died who had received less than 350 c.c. of blood.

The present case is reported as unusual, in that recovery followed transfusion of 750 c.c. of blood, and that it seemed to depend on venesection, a measure not evidently used in previous cases reported.

Case Reports

Mrs. B., aged 32, wife of a physician, was the mother of three children, and had had one spontaneous abortion; all her pregnancies had been free of toxic symptoms, save for moderate hyperemesis during one of them; her labors had all been normal.

Her previous medical and surgical history was negative except for appendicitis with appendectomy six years before the present illness.

Following her last parturition six months ago, she had complained constantly of general malaise, weakness and coldness of the body surface, and a loss of 20 pounds in weight; there was a moderate anemia of secondary type: hemoglobin 65 per cent; red blood cells 3,600,000; white blood cells 8000. The urinalysis was normal. No satisfactory explanation of the cause of her anemia had been found. Various methods of therapy had not improved her condition, and it was hoped transfusion might do so.

She was admitted to Christ Hospital for this purpose June 4, 1931.

Blood count on admission was: hemoglobin 70 per cent, Sahli; red blood cells 4,200,000; white blood cells 7000; polymorphonuclears 70 per cent; lymphocytes 30 per cent. The blood was designated a Type II Jansky by two different laboratories. Cross matching between the donor and the recipient showed no hemolysis or agglutination.

Operation. Transfusion was begun at about 1:00 p.m., June 5, 1931. Seven hundred and fifty cubic centimeters of whole blood were given by the Unger method. During the operation, the patient made no complaint; subsequently, she stated that a headache developed towards the end of the transfusion.

A sharp febrile reaction occurred which reached its maximum (103° F.) seven hours after transfusion and receded to normal in 18 hours. For the remainder of her stay in the hospital, the temperature was within normal limits.

During this period of reaction, severe occipital headache, and intense pains in the limbs and lumbo-sacral region occurred. She felt nauseated and vomited several

* Received for publication November 11, 1932.

times. The vomitus contained blood. A small quantity of urine was voided but, unfortunately, its characteristics were not charted.

June 6th: The pains in the limbs and back are not so intense. The occipital headache has not lessened. Pain and tenderness are especially referred to both mastoid regions. Movements of the head are resisted; the neck is slightly rigid. Nausea continues and a greenish-brown fluid was vomited once during the day. Urinary output for the twenty-four hours only 200 cubic centimeters. It contained much blood.

June 7th: During the early morning hours, the patient twice vomited a large quantity of bloody fluid. Pain in the mastoid regions is complained of constantly and bitterly. Urinary output 150 cubic centimeters; albumin 4 plus; many red blood cells; many shadow cells. These findings were regarded as indicating a combination of hematuria and hemoglobinuria. Blood count—hemoglobin 87 per cent Sahli; red blood cells 4,600,000; white blood cells 17,200; polymorphonuclears 92 per cent; lymphocytes 8 per cent.

June 8th: The pains have somewhat diminished. In the right hypochondriac region, the kidney is palpable, feels enlarged and is tender on pressure. Urinary output 300 cubic centimeters with the same characteristics as the day before. Blood pressure 115 millimeters of mercury systolic and 80 diastolic.

Examination of the optic fundi revealed no blurring of the discs, exudates, or hemorrhages. Both tympanic membranes were normal. Blood chemistry—urea N 50 mg.; creatinine 3.7 mg.; uric acid 2.8 mg.; sugar 90 mg.

June 9th: Except for occasional nausea, the patient spent a fairly comfortable day. Urinary output, 250 cubic centimeters.

June 10th: Complains less of pain and nausea. One thousand four hundred cubic centimeters of fluid were retained by mouth and rectum. Voided 600 cubic centimeters. Vomited 200 cubic centimeters of fluid; the vomitus contained no blood. Blood chemistry—urea N 66.6 mg.; creatinine 7.5 mg.; uric acid 3.8 mg.; sugar 100 mg. Spent a fairly comfortable day.

June 11th: Occipital headache has increased in severity. The neck is more rigid. A fine petechial rash has appeared over the abdomen, back and arms. Blood pressure 140 millimeters of mercury systolic and 80 diastolic.

Blood chemistry—urea N 72 mg.; creatinine 7.8 mg.; CO_2 combining power 63.3 volumes per cent. Fluid intake 1700 cubic centimeters; urinary output 550 cubic centimeters. It contained no blood.

June 12th: Outstanding symptoms, occipital headache and rigidity of the neck. Vision is impaired; complains of blurring and loss of sight. Ophthalmoscopic examination is negative. Reflexes are somewhat hyperactive. Babinski and Kernig signs are absent. Lumbar tap—10 cubic centimeters of spinal fluid withdrawn; no increased pressure; clear; cell count 2; sugar reduction 3 plus; globulin negative; smear and culture negative. Electrocardiogram negative.

At 11:30 p.m. the patient had a generalized convulsion lasting one minute. Fluid intake for the day 1250 cubic centimeters; urinary output 950 cubic centimeters, no blood.

June 13th: At 1:00 a.m. the patient had a generalized convulsion; later vomited and complained of severe frontal headache and vertigo. At 3:45 a.m. had another convulsion.

From 5:45 a.m. until 7:45 a.m. had many convulsions with short intervals of coma. Intravenous glucose, intravenous and intramuscular magnesium sulfate had been administered but with no marked benefit. Her condition was deemed desperate and we decided to bleed her.

Phlebotomy was performed and 450 cubic centimeters of blood withdrawn. Five hundred cubic centimeters of normal saline were introduced into a vein after the venesection. Blood chemistry of the phlebotomized blood—urea N 75 mg.; creatinine 7.5 mg.

Immediately after the venesection, convulsions ceased, consciousness returned shortly, and the general condition greatly improved. During the day she slept for long intervals and asked for nourishment. Diuresis increased to 2500 cubic centimeters.

Blood count after the venesection: hemoglobin 50 per cent Sahli; red blood cells 2,890,000; white blood cells 18,600; polymorphonuclears 92 per cent; lymphocytes 8 per cent.

June 14th: Patient feels comfortable, except for slight attacks of momentary nausea and blurring of vision. Diuresis has increased to 3000 cubic centimeters.

June 15th: Diuresis continues and subsequently urinary output was normal while the patient remained in the hospital.

June 19th: Blood chemistry—urea N 30 mg.; creatinine 2.7 mg.; uric acid 2.5 mg.; sugar 120 mg.

June 25th: Blood chemistry—urea N 10 mg.; creatinine 1.5 mg.; uric acid 2.1 mg.; sugar 90 mg. Urine sp. gr. 1.013; albumin, trace; very occasional red blood cells and white blood cells.

June 26th: Patient discharged from the hospital.

Subsequent History. About five months after leaving the hospital, she had an attack of pain in the right hypochondriac region. This was accompanied by nausea and headache. The right kidney was palpable and tender. Only 30 cubic centimeters of urine were voided in twenty-four hours. The sp. gr. of the urine was 1.020, faint trace of albumin, no casts.

During the next day, the symptoms promptly subsided with the excretion of a large amount of urine.

A pyelogram taken shortly after this attack revealed a slight kink in the right ureter.

Comment

This case conforms in its major clinical manifestations and course to the group of cases cited by Bordley. The presumption is that the reaction noted depended on blood incompatibility. The recipient had been repeatedly typed as a Group II Jansky before operation, and the donor conformed to the same type by tests before and after the transfusion. The bloods were cross-agglutinated before operation without evidence of hemolysis or agglutination, but it is certain that this reaction was not observed for as long as two hours, which was the length of time before Bordley's first case did show slight agglutination on retest. Herein probably lies the source of error. Unfortunately, cross-agglutination was not subsequently repeated in this case.

The recipient's history and previous clinical observation showed nothing to indicate preëxisting nephritis. The donor's urinalysis and blood chemistry were normal.

It is not believed that the reflex anuria noted some months later, possibly dependent on kinking of the ureter seen in the pyelogram, was related to the condition following transfusion. It was transient, not accompanied by any evidence of nephritis or uremia, but was manifested by localizing symptoms not present during the more severe illness.

Inasmuch, however, as in the cases previously described there was no observation of anatomical anomalies, there might be speculation as to whether the existence of such lesions may contribute in any degree to insufficiency of the kidney due to blood incompatibility.

Summary

1. A patient was transfused with 750 cubic centimeters of whole blood for secondary anemia.

2. An immediate reaction occurred as evidenced by the sharp rise in temperature accompanied by hematuria, hemoglobinuria and oliguria.

3. A delayed reaction occurred which reached its peak on the ninth day. This reaction was characterized by severe uremic symptoms; headache, rigidity of the neck, convulsions and coma. Repeated blood chemistry examinations during this period showed marked urea-nitrogen and creatinine retention, clinical and chemical evidence of renal insufficiency.

4. Venesection of 450 cubic centimeters of blood followed by the introduction of 500 cubic centimeters of normal salt solution intravenously, resulted in an immediate cessation of uremic symptoms.

5. Venesection as a method of treatment in renal insufficiency following blood transfusions has not been suggested or employed in cases reported in the meager literature on this subject to which we have had access.

6. The subsequent attack of reflex anuria brings up the question of a mechanical factor in the development of renal insufficiency following blood transfusion.

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VITAMIN THERAPY IN PULMONARY TUBERCULOSIS*

IV. COMPARISON OF THE H-ION CONCENTRATION OF THE BLOOD IN TUBERCULOSIS WITH NORMALS ON THE SAME DIETARY

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In studying the effect of vitamin D upon the calcium equilibrium of the human body infected with tubercle bacilli, normal chemical relationships are prerequisite. A normal blood calcium and phosphorus is interwoven in the physico-chemical complex of a normal acid-base balance. One of the factors representing this balance is the H-ion concentration of the blood. That H-ion concentrations within normal limits exist during the clinical course of many diseases is obvious, otherwise they would present to us an accompanying state of acidosis or alkalosis. Although bio-chemical tests other than pH give us a wider range of analysis and interpretation, yet the pH test interpreted with its accompanying variables makes this analysis an added criterion.

Method

Electrometric methods for determining the pH of the blood plasma are too intricate and expensive for universal use. Several investigators have proved the accuracy of the glass electrode method for determining the H-ion concentration of the blood. Fosbinder and Schoonover [1] of the Cancer Research Laboratories under the direction of McDonald [2] made a comparative study of the glass electrode and colorimetric method of Hastings and Sendroy.[3] Hastings and Sendroy [3] previously had improved Cullen's [4] method. Fosbinder and Schoonover [1] found the average deviation between the two methods to be 0.002. McDonald's [2] modification of Hastings and Sendroy's [3] method was used in making the following analyses of blood plasma.

Experimental Requirements

Investigators in recent years are becoming more cognizant of the many physiological and chemical factors which might influence any analysis of the blood's constituents. For example, much previous work on serum calcium has been performed with disregard for calcium and phosphorus in the

* Received for publication November 11, 1932. From Boehne Tuberculosis Hospital, Evansville, Indiana.

dietary intake. Disregard of this one factor alone causes many interpretations to disagree. Whether the delicate pH test of the blood plasma will demand certain specific requirements in the diet for comparative analysis, is still a conjecture. At any rate, in this comparison, the normals and those patients infected with pulmonary tuberculosis, were on the same routine dietary. All analyses were performed during the months of May, June, and July. All determinations were performed by the same chemist. Bloods, for the most part, were drawn between the hours of 2 p.m. and 5 p.m. and examined immediately. This time of determination was considered satisfactory because the average of 22 determinations at 9 a.m., 28 determinations at 2 p.m. and 34 determinations at 5 p.m. gave an average pH of 7.38 for each time group. This average does not represent a pH time element for a single day. Several patients had three determinations at 9 a.m., 2 p.m. and 5 p.m. over a ten-day period and were also found to have an average pH of 7.38.

Data

The following analyses were performed prior to the investigation of hypercalcemias. Table 1 lists the pH of 50 normal individuals. The average range of this normal group was 7.35 to 7.40. The average normal pH was 7.37. McDonald and co-workers [2] reported an average normal pH of 7.38 on 25 patients from November 1928 to January 1931. If we compute the probable error according to the formula $E = .67\sqrt{\frac{\Sigma v^2}{n\,(n-1)}}$

Table I

List of Normal pH Values

No.	Age	Sex	pH	No.	Age	Sex	pH
1	24	M	7.38	27	23	F	7.38
2	23	M	7.39	28	19	F	7.39
3	48	F	7.36	29	23	M	7.39
4	27	F	7.39	30	43	M	7.37
5	21	F	7.38	31	18	F	7.38
6	45	F	7.40	32	21	F	7.36
7	36	F	7.36	33	25	F	7.37
8	22	F	7.38	34	46	M	7.38
9	45	F	7.39	35	56	M	7.39
10	22	F	7.38	36	22	F	7.37
11	21	F	7.37	37	58	M	7.37
12	47	F	7.38	38	29	F	7.39
13	19	F	7.39	39	23	F	7.38
14	35	F	7.37	40	24	F	7.37
15	21	F	7.39	41	27	F	7.37
16	40	M	7.40	42	19	F	7.39
17	22	F	7.39	43	19	F	7.36
18	19	M	7.37	44	18	F	7.37
19	18	F	7.36	45	23	F	7.38
20	23	F	7.37	46	18	F	7.40
21	24	F	7.38	47	18	F	7.38
22	59	M	7.37	48	24	F	7.36
23	35	M	7.35	49	26	F	7.38
24	52	M	7.36	50	29	F	7.37
25	25	F	7.38				
26	18	F	7.37			Average =	7.37

for the group of pH normals, the coefficient of variation equals .001, which is well within the limits of experimental error. According to Hastings and Sendroy [3] this method permits the estimation of colorimetric pH values to within $\pm$ .02.

Table 2 lists the pH of 75 patients in various stages of pulmonary tuberculosis. The average pH range for these patients with pulmonary tuberculosis was 7.33 to 7.45, the average being 7.38. If we compute the probable error according to the formula $E = .67\sqrt{\frac{\Sigma v^2}{n\,(n-1)}}$ for this group of pH determinations, the coefficient variation equals .0006, which is well within the limits of experimental error.

TABLE II

List of pH Values in Pulmonary Tuberculosis

No.	Age	Sex	Mean Temperature F.	pH
		STAGE I		
1	46	F	98.6	7.37
2	22	M	98.6	7.39
3	37	M	98.6	7.38
4	29	F	98.8	7.38
5	19	M	98.6	7.39
6	34	F	98.8	7.37
7	21	M	98.6	7.39
				Average = 7.38
		STAGE II		
8	35	M	98.8	7.39
9	42	M	98.6	7.39
10	25	F	98.6	7.38
11	17	F	98.8	7.37
12	24	M	98.6	7.36
13	27	F	98.8	7.35
14	44	F	99.0	7.39
15	37	M	99.0	7.39
16	17	M	99.6	7.40
17	42	F	99.0	7.36
18	27	F	99.0	7.39
19	20	M	98.8	7.39
20	26	F	99.4	7.42
21	34	F	98.8	7.38
22	24	F	98.8	7.38
23	14	F	98.8	7.37
24	19	F	99.0	7.39
25	28	F	99.0	7.39
26	28	F	99.4	7.40
27	18	F	98.8	7.34
28	16	F	99.0	7.36
29	24	F	98.6	7.37
				Average = 7.38

TABLE II (*Continued*)
List of pH Values in Pulmonary Tuberculosis

No.	Age	Sex	Mean Temperature F.	pH
		STAGE III		
30	24	F	99.6	7.38
31	27	F	99.2	7.38
32	25	M	99.0	7.37
33	28	M	98.8	7.39
34	35	F	98.8	7.39
35	27	M	99.0	7.38
36	39	M	99.6	7.33
37	17	F	100.6	7.42
38	45	M	98.6	7.38
39	17	M	98.8	7.38
40	20	F	99.4	7.37
41	54	M	99.6	7.36
42	30	F	99.2	7.43
43	14	F	101.0	7.42
44	31	F	99.2	7.37
45	33	M	99.0	7.37
46	39	F	99.0	7.40
47	41	F	99.6	7.37
48	38	F	99.0	7.45
49	41	F	99.2	7.36
50	22	F	100.0	7.37
51	19	M	99.0	7.37
52	55	M	98.6	7.39
53	27	M	99.2	7.35
54	54	M	100.0	7.42
55	28	M	98.0	7.34
56	35	F	99.6	7.35
57	17	M	99.0	7.39
58	14	M	99.6	7.43
59	29	F	101.0	7.45
60	40	F	99.4	7.42
61	18	F	99.0	7.37
62	55	F	99.6	7.44
63	45	M	99.0	7.42
64	44	M	99.6	7.39
65	48	M	99.4	7.39
66	28	M	99.4	7.37
67	48	M	100.0	7.43
68	30	M	100.0	7.40
69	30	F	99.6	7.40
70	22	F	99.6	7.39
71	27	F	99.4	7.39
72	61	M	99.2	7.42
73	26	M	98.6	7.39
74	26	F	99.8	7.39
75	35	F	99.2	7.41
			Average =	7.39
			Total Average =	7.38

COMMENT

Patients with pulmonary tuberculosis showed a slightly increased pH of the blood when compared with normal individuals. The group in Stage I is afebrile. The average pH for this group in 7.38. In the Stage II group, there were slight elevations of temperature. It so happened that

each patient that had a temperature of at least 99.4° also had a pH of 7.40 or more. The average pH for this group is 7.38. However, in the Stage III group, several patients with 99.4° had a pH under 7.40 but all the patients in this group except one, that had a temperature of 100°or more, had a pH ranging from 7.40 to 7.45. The average pH for this Stage III group is 7.39.

Other factors being equal, it is apparent that the febrile condition accompanying patients with pulmonary tuberculosis in Stage II, and particularly those in Stage III, was responsible for the slightly higher elevation of the pH. Kast, Myers and Schmitz [5] found the pH somewhat higher than normal in febrile patients. Peters and Van Slyke [6] in summarizing their work [5] and that of others done on pH and CO_2 content of the serum in febrile patients say, ". . . one cannot conclude with certainty that in the cases reported the cause of the observed effects on the acid-base balance was the fever rather than other influences of the diseases." The patients in this series who had a temperature of 100° or more had an average pH of 7.41. In our opinion the disease of pulmonary tuberculosis, other metabolic processes being normal, affects very little, if any, the H-ion concentration of the blood unless a febrile condition exists.

Summary

The average normal pH performed on 50 normal individuals is 7.37. The average pH performed on 75 patients in various stages of pulmonary tuberculosis is 7.38.

It is also significant to note that a slightly wider range of pH existed in patients with pulmonary tuberculosis, namely a pH of 7.33 to 7.45 against the normal's range of 7.35 to 7.40.

It is apparent that the febrile condition accompanying patients with pulmonary tuberculosis is responsible for a slightly decreased H-ion concentration (pH increased).

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THE CLINICAL VALUE OF THE PRESUMPTIVE KAHN TEST*

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SOON AFTER the development of the standard Kahn reaction in 1923, Dr. Kahn proposed a more sensitive method, which he named the Presumptive test, to be employed as a check on the standard method.[1] Since that time the standard reaction has become an accepted method throughout the world. The same cannot be said, however, in the case of the presumptive reaction. One finds comparatively few reports in the literature on this reaction, indicating that it is relatively little used. The reason for this may be the fact that serologists who often employ the Kahn with the Wassermann test have the feeling that two tests are sufficient. Then again, some serologists prefer to resort to precipitation methods, such as the Kline or Meinicke tests, if they wish a check of the Wassermann and Kahn reactions.

In our own laboratory, it has been our practice to use the Wassermann and Kahn tests routinely. About three years ago, we added the presumptive Kahn to these two tests and we believe that we have increased the correctness of our serologic results during this period to an extent that more than compensates for the effort and expense in performing this test.

Let us first consider the results with the presumptive Kahn test reported by other workers.

McDermott[2] in a study of 15,000 cases found the presumptive test to be 2 per cent more sensitive than the regular Kahn in the general run of hospital cases and 26 per cent more sensitive in treated cases of syphilis. In a comparative study of 1300 spinal fluid Kahn tests, the same worker found the presumptive to be 12 per cent more sensitive than the standard Kahn in the general run of hospital cases and 18 per cent more sensitive in treated cases of neurosyphilis.

In a clinical study of the standard and presumptive Kahn reactions in neurosyphilis made by Davenport,[3] the standard reaction with spinal fluid was found to be highly specific for neurosyphilis, but it occasionally gave a negative reaction in the presence of this clinical condition. Thus in 118 untreated cases of neurosyphilis, two negative standard Kahn reactions were obtained and in 369 treated cases of neurosyphilis, 23 negative standard Kahn reactions were obtained in patients who required further central nervous system therapy. Turning to the presumptive procedure, however, of 115 positive reactions obtained in a group who have received no treatment for neurosyphilis, 13 were obtained in syphilitic patients who showed no clinical evidence of neurosyphilis. In other words, all positive spinal

* Received for publication January 23, 1933.

fluid reactions given by this method were cases of syphilis and it may indeed be that this test is the earliest indicator of neurosyphilis available today, giving positive reactions long before there are clinical manifestations of this condition. With regard to treated cases of neurosyphilis, Davenport reports 30 positive spinal fluid reactions on patients who clinically required no further therapy to the central nervous system, and four negative reactions on patients who, although apparently well and at work, were in need of further treatment as a factor of safety. In short, the presumptive spinal fluid test seemed to be far more sensitive than the standard Kahn test both in untreated and in treated cases of neurosyphilis.

Turning to the results of the presumptive test at the Montevideo conference,[4] it might perhaps be well to first emphasize that this conference was competitive in nature to the same extent as the Copenhagen conference. Bloods were collected from known cases of syphilis and from non-syphilitic controls in various hospitals of Montevideo as well as in medical centers of Buenos Aires and Rio de Janeiro from where they were sent by air mail to the Prophylactic Institute of Montevideo where the conference was held. A total of 927 serums were examined. Of these, 623 came from cases of syphilis, including all stages, both treated and untreated. The remaining 304 came from non-syphilitic persons, most of whom, however, suffered from some pathological condition other than syphilis.

Table 1 was taken from the official report of the League of Nations' Health Committee of the Montevideo conference. It is evident from this

TABLE I

The Results Obtained by the Various Methods at the Montevideo Conference, Expressed on a Percentage Basis

(From League of Nations, Health Organization, Report of Montevideo Conference, Geneva, 1931)

Method	Percentage Syphilis	Positive Reactions Non-syphilitic Controls
		One per cent or less of non-specific reactions
Kahn's "presumptive" test	75.6	1.0
Muller's clotting test (M. B. R. 11)	69.3	0.7
Kahn's "standard" test	63.9	0
Modified B.-W. test performed by Sordelli and Miravent	55.9	0
Modified B.-W. test performed by Wyler	54.4	0
Modified B.-W. test performed by Scaltritti and Cassiniga	49.9	0
		More than 1 per cent of non-specific reactions
Modified B.-W. test performed by Moreau	64.7	13.9
Meinicke's clarification test (M. K. R.) performed by Dussert-Jelland	62.2	2.4
Modified B.-W. test performed by Torrazza and Lorenzo	55.5	2.6
Modified B.-W. test performed by de Assis	54.9	4.3
Sero-haemo-flocculation test performed by Prunell	52.4	4.5
Modified B.-W. test performed by Puppo	45.4	5.6

table that the presumptive test was more sensitive than the other methods employed, giving 75.6 per cent positive reactions while some methods in the same group of syphilitic cases gave as low as 45 to 50 per cent. With regard to positive reactions obtained in non-syphilitic cases, only four methods were free from such reactions: the Kahn standard reaction and three Wassermann methods; these three, however, were considerably less sensitive than the Kahn reaction. The remaining eight methods gave varying numbers of false positive reactions. The presumptive test gave 1 per cent, and the other seven methods gave from 0.7 to 13.9 per cent of such reactions. It is evident that the presumptive test, in spite of its high specificity, gave a relatively small number of false positives at that conference.

Table 2 presents in actual figures the increase in sensitivity of the presumptive over the other tests at the Montevideo conference. Of 623 treated

TABLE II

The Results of the Presumptive Kahn Test at the Montevideo Conference

Wherein this test was compared with 7 different Wassermann tests and 4 precipitation tests in the examination of 623 cases of syphilis (untreated and treated) and 304 non-syphilitic controls.

Method	Performed by	No. of Positive Reactions in Syphilitic Group	Increase in Sensitivity of Presumptive over Other Tests	No. of Positive Reactions in Non-Syphilitic Group
Presumptive	...Kahn (University of Michigan, Ann Arbor)	471		3
Standard Kahn	..Kahn (University of Michigan, Ann Arbor)	398	18%	None
Wassermann	...Sordelli (Nation Bact. Inst., Buenos Aires)	347	36%	None
Wassermann	...Harrison-Wyler (Ministry of Health, London)	339	39%	None
Wassermann	...Scaltritti (Prophylactic Inst., Montevideo)	311	51%	None
Wassermann	...Torrazza (Medical School, Montevideo)	346	36%	8
Wassermann	...deAssis ("Vital Brazil" Inst. Rio de Janeiro)	342	38%	13
Wassermann	...Puppo (Sanit. Military Service, Montevideo)	283	66%	17
Wassermann	...Moreau (Medical School, Montevideo)	402	17%	42
Meinicke MKR	.Dussert (Nat'l Bact. Inst., Santiago)	387	21%	7
Prunell	.....Prunell (Nat'l Health Dept., Montevideo)	330	44%	14
Muller MBR 11	.Muller (General Hospital, Vienna)	432	9%	2
	Average increase in sensitiveness of the Presumptive Test		34%	

and untreated syphilitic cases examined, the presumptive test gave 471 positives, while the number of positives given by the other methods varied from 283 to 432. When one considers the average increase in sensitiveness of the presumptive test over all of the other methods tested at Montevideo, one finds it to be 34 per cent.

We have adopted the practice in this laboratory, whenever confronted with negative standard Kahn and Wassermann tests and positive presumptive reactions, of routinely communicating with the clinician who submitted the specimen. In each instance where it was possible to obtain the correct history or when it was possible to study the patient more fully, it was ultimately established that the positive presumptive test was a specific reaction.

Table 3 gives the results of the presumptive test in comparison with the standard Kahn and Wassermann tests in 3,182 cases. Of this number

TABLE III

Increase in Sensitivity of Presumptive Kahn Test over the Standard Kahn and the Wassermann Tests in a Group of 3,182 Cases

No. of Cases	Presumptive Kahn Test	Standard Kahn Test	Wassermann Test
498	+++, ++++	+++, ++++	+++, ++++
89	+++, ++++	++, +++	+, ++
87	+++, ++++	+, ++	−
79*	+++, ++++	−	−
97*	+, ++	−	−
2332	−	−	−

Per cent Positive by all Methods	18.4
Per cent Negative by all Methods	73.3
Per cent Positive by Presumptive and Standard Kahn and Negative by Wassermann	2.7
Per cent Positive by Presumptive Kahn and Negative by Standard Kahn and Wassermann	5.5

* Of this group of 176 patients, 70.4 per cent (124 cases) represent patients under treatment; 7.4 per cent (13 cases) were diagnosed as syphilis—9 patients in this group were in the primary stage with positive dark-field findings; 22.1 per cent (39 cases) were undetermined, we having been unable to secure definite data as to the presence or absence of syphilis.

there was complete and relative agreement in 2,830 cases. Eighty-nine strongly positive presumptives gave moderately positive standard Kahn and weakly positive Wassermann tests. Eighty-seven strongly positive presumptives gave moderate and weakly positive standard Kahn tests with negative Wassermann tests. We are not concerned about this group of cases because of the well known specificity of the standard Kahn test. What concerns us especially is the group of 176 patients who gave positive presumptive tests and negative tests with the other two methods. Of these 176 patients, 124 (70.4 per cent) were under treatment for syphilis: 13 (7.4 per cent) were cases presenting themselves for diagnosis who had not as yet received treatment. Nine of these 13 cases were in the primary stage with positive dark-field findings. The remaining 39 cases (22.1 per cent) were undetermined, we having been unable to secure definite data as to the presence or absence of syphilis. Of the 97 cases listed in the table as one plus or two plus reactions, the vast majority were two plus reactions. From the facts presented in this table it is evident that the presumptive Kahn test detected significant reactions in 137 cases of syphilis during the past three

years that would not have been detected by the standard Kahn and Wassermann tests.

There is some controversy today as to when treatment should be discontinued and there are some syphilologists who believe that it is not essential to treat the patient until all serological evidence of syphilis has disappeared. It has been most interesting to us in this study to notice that among the patients who continued to receive treatment for some weeks after the presumptive Kahn became completely negative, not one has shown any symptoms of syphilis or any serologic evidence of this disease; while those patients who have discontinued treatment while the presumptive reaction was still partly positive frequently on subsequent check up have shown definite positive reactions by all methods employed.

Before closing, I should like to quote the statement of a well known pathologist regarding the presumptive reaction. The late Dr. Aldred Scott Warthin who was a student of syphilis for thirty-five years, made the following statement in his lecture "The Problem of Latent Syphilis" before the Institute of Medicine of Chicago (November 21, 1930) [5]:

> The correlation between the tissue lesions and the serological reactions offers very definite problems. There was only about a 50 per cent agreement between the Wassermann reaction and the histologic findings in our cases. During the last two years the Kahn reaction has been used in our hospital with a much higher per cent of agreement. In the case of the presumptive Kahn, with a more sensitive antigen the agreement has reached about a 97 per cent degree. In several cases with a four plus presumptive Kahn, the clinicians have wholly denied the possibility of the patient having syphilis, when on autopsy a very active syphilitic aortitis was found. In our experience then, the Kahn test shows a much higher degree of accuracy when checked with the microscopic findings than does the Wassermann. We have had no false positives, and but few negatives.

Conclusions

1. The presumptive Kahn test is an extremely sensitive method for the detection of syphilis.
2. In 3182 examinations of blood the presumptive test was found to be more sensitive by 8.2 per cent than the Wassermann test and more sensitive by 5.5 per cent than the standard Kahn test.
3. The presumptive test appears to possess also a high degree of specificity and furnishes a valuable addition to the standard Kahn and Wassermann tests in the detection of syphilis.
4. The presumptive test is of value as a criterion in establishing the absence of syphilis. Due to the high sensitivity of the presumptive test, it is obvious that a negative reaction by this method has greater significance than a similar reaction given by less sensitive methods.
5. A great deal of valuable information may be gained by the use of the presumptive test as a check on other reactions for syphilis.
6. The presumptive test is of special value in primary syphilis, latent syphilis, neurosyphilis and in determining when to discontinue treatment.

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THE SOURCE OF MODERN MEDICINE*

An Address to the American College of Physicians

By Sir Andrew Macphail, *Montreal, Canada*

Gentlemen: I must trouble you with a date, 1685, the year in which Charles II died. That reign marks the watershed between the medieval and the modern world; between the mass and the individual; between authority and experience; between books and experiment. From that summit the spring of modern medicine burst forth.

It was in reality a new world. The Royal Society had been founded; the circulation of the blood had been proved; the Cartesian method had been disclosed; the universal law of gravity and the laws of planetary motion had just been announced. Logarithms, electricity, magnetism, chemistry were words coming into common use.

Up to that time, the authority in science was Aristotle; in philosophy, Thomas; in medicine, Galen. All three had organized and synthesized the existing knowledge of their day. It was a useful task; but when life is too closely organized it begins to perish. The body of knowledge then becomes a burden, a tradition; it blinds men's eyes; it makes them incapable of observation or thought. It enslaves them; but suddenly, freedom asserts itself. Freedom too has perils, but they are less dangerous than the perils of slavery. One can now say what he likes, even in medicine, no matter how foolish; there will be plenty to contradict him.

There were reasons deeper still for the scientific renascence of the period under review. The divine right in science of Aristotle and the Greeks had passed; the divine right of kings in politics perished at the hand of Cromwell; the divine right of Galen in medicine came to an end with the appearance of Thomas Sydenham; and so we have come to our subject at last.

For a perfect sight of the old medicine, let me conduct you to the bedside of Charles II: With a cry he fell. Dr. King who, unfortunately, happened to be present bled him with a pocket-knife. Fourteen physicians were quickly in attendance. They bled him more thoroughly; they scarified and cupped him; they shaved and blistered his head; they gave him an emetic, a clyster, and two pills. During the next eight days they "threw in" 57 separate drugs; and, towards the end, a cordial containing 40 more. This availing nothing, they tried Goa stone, which was a calculus obtained from a species of Indian goat; and as a final remedy, the distillate of human skull. In the case report it is recorded, that the emetic and the purge worked so mightily well, it was a wonder the patient died. One physician did protest that they would kill the king; and out of this arose the suspicion that he had

* Read before the American College of Physicians, Montreal, Canada, February 8, 1933. From McGill University, Montreal, Canada.

been irregularly poisoned. But he did die, "as peaceable as a lamb"; his last words were, "Do not let poor Nellie starve."

While this medieval practice was in progress at the palace, not far away, on the north side of Pall Mall, looking south over St. James' Park, opposite to Nellie's, and quite near the house of Moll the dancer, lived Thomas Sydenham. But he was not called to the royal bedside. He was a Puritan; he had been a captain of horse in the parliamentary army; and, worse still, he was reputed to be practising medicine "in a new way." Out of his specifically creative mind modern medicine was already emerging by this new way.

His method was no secret. Twenty years ago, he had published his method of curing fevers; he was ready to publish his Observations, a series of five letters addressed to friends: "about the sum of all I know of the cure of disease up to the day on which I write, namely the 29th September, 1686." He died three years later. A collection of letters to his son was issued after his death. That is all. He lies buried in the church of St. James', Piccadilly, where a mural tablet was put up by the Royal College of Physicians in 1810. It bears the inscription adapted from Horace, *Medicus in omne aevum nobilis*,—a physician famous for all time.

The most casual reading of his little books reveals the method. There is no dogma, no system, no body of doctrine, merely a few general principles. It is not a method even; it really indicates a way of looking at things, without searching too curiously into their causes. He looked upon diseases as they appeared to him, and made a complete study of each.

Most forms of disease, he thought, had a definite and uniform type due to the uniformity of the cause. He sought only for the "evident and conjunct causes"; the remote ones he thought it vain to seek. Acute disease he considered to be a reaction of the body to meet some injurious influence coming from without. He was content to watch and aid in the natural crisis. Chronic diseases were in the main due to errors in diet and in the general way of life. As he put the case, "Acute disease is an act of God; of chronic disease the patient himself is the author."

Fever was nature's engine against the enemy, or her handmaid for removing the morbific material from the blood. Fever was a sign that nature was curing the disease, and should not be curbed unless it becomes too violent. The patient should be lightly covered; he should be allowed air and light, with water if he was thirsty, and food only when his appetite demanded it.

To do without hypotheses, and study the actual disease with an open mind; to make an unbiased study of the natural processes in health and disease; to trust in the healing power of nature—for nature is the mother and healer of us all—and provide help only when help was demanded,—that was his re-discovery, for the original discovery had been made by Hippocrates himself.

He demanded that a physician should regard disease with the eye of a naturalist, and describe it with equal care. "If only one person in every

age," he said, " had accurately described and habitually cured only one single disease, and disclosed his method, physic would not now be where it is." Every hypothesis must be abandoned, while every phenomenon of disease is being minutely observed; " but it is right and necessary to distinguish between the constant characteristics of a disease and those that are merely accidental and adscititious. Want of accuracy in distinguishing diseases that are apparently similar is fatal to medicine."

Sydenham, of course, had his own theories; but he was never enslaved by them. Still less was he enslaved by classical dogma or by the chemical theories then in vogue. He made his own the great saying of his favorite, Bacon: We have not to imagine or to think out, but to discover what nature does. These are the very words that Hunter addressed to Jenner, Do not think—try.

In practice Sydenham did not disdain the use of drugs; he used Peruvian bark freely, as well as laudanum which he was the first to prepare; but he had many cases, " in which he consulted his patient's safety and his own reputation most effectually by doing nothing at all." It was a great mistake, he declared, to suppose that nature always needed the assistance of art. His friend, John Locke, the philosophical father of Hume and Kant, himself a captain in the army of the parliament, and a practising physician as well, in commending the new method writes to a friend, " You cannot imagine how far a little observation will carry a man in the curing of disease, though very stubborn and dangerous, and that with very little and common things, and almost no medicine at all."

Too much has been made of Sydenham's contribution to the diagnosis of disease. True, he distinguished between chorea and St. Vitus dance; he described syphilis, and recognized many diseases as specific in the modern sense; he established hysteria as a definite disease; his description of gout remains unexcelled. It was from that malady he suffered and died; but he consoled himself with the reflection, that fools rarely suffer from it, unless indeed he himself might have been an exception. He missed many of the symptoms of scarlatina; and his classification of fevers remains obscure.

It was in practice he excelled. For a patient who had suffered from the prevailing lowering treatment he prescribed a roast chicken and a pint of canary wine. A hypochondriac he advised to consult a physician in Inverness. The man proceeded on horseback; he could not find the doctor; he returned very angry but cured. " Nothing," Sydenham said, " so cherishes and strengthens the blood and spirits as riding a horse."

In addition to all this, there was in Sydenham, as there was in Hippocrates, in Pasteur, and in Lister, a powerful moral element which shines on every page. " Whoever," he wrote, " applies himself to medicine ought seriously to consider: first, that he will one day have to render an account to the Supreme Judge of the lives of the sick committed to his care; and next, that whatever skill or knowledge he may, by divine favor, possess should be devoted above all else to the glory of God and the welfare of hu-

manity." And again, "the physician will care for the sick with more diligence and tenderness if he remembers that he himself is a fellow-sufferer."

Sydenham created no great stir in London. To the end of his days he remained on the outside of the faculty, although he had his friends within and without, and in that Invisible College which was the precursor of the Royal Society. To us who are alert for any new method the conduct of the profession towards Sydenham seems strange: For thirty years he was described as a "sectary." In one of the few letters now extant, written in English, he admits that, "while he has the happiness of curing his patients, some of the faculty take fire at his attempts to reduce practice to a greater easiness." In another letter he utters a mild protest against those who make it a matter of reproach, if one brings forward anything new, which had not previously been said, or heard, by themselves.

But the profession must not be too severely blamed. We are so often right in our skepticism, we may be forgiven when we are occasionally wrong. And Sydenham was quite "irregular." He practised in London until he was forty years old, without a license of any kind. In 1663 he was admitted licentiate by examination of the Royal College of Physicians, which is the lowest rank. It was not until 1676 that he acquired the doctor's degree, not from Oxford but from Cambridge. He was at the time 52 years old, and his son was an undergraduate there. He is known to have had the degree of bachelor of medicine from Oxford, but there is no official record. In any case, his medical study must have been short, and not profound. To compensate, he is alleged to have taken a postgraduate course at Montpellier. There is no evidence of that either, although French writers make the most of the legend through the natural desire to claim him as their own.

Even his unlicensed practice was interrupted by an excursion into politics in 1658, when he became a candidate for parliament. He was unsuccessful; but as a defeated candidate he was appointed Comptroller of the Pipe, an office long since obsolete, and having to do with crown lands. More important, he was awarded 600 pounds on account of his military service. With this money in hand he married, and settled down to practise medicine.

Likewise, his study preliminary to medicine was brief. He entered Oxford at the age of eighteen; but after three months his career was interrupted by the outbreak of civil war. He joined the army in company with three of his brothers; he kept the field for four years, when he returned to the University, and received an academic degree in 1646. Two years later, after his return from the second civil war, he was made Bachelor of Medicine by "actual creation." It was an honorary degree given in advance of the study for a profession which he entered by the influence of "a great man and by his own destiny."

It was quite natural, therefore, that he should be considered in London as an uneducated and unqualified person. He could not write Latin, although he could read it; his writings must be translated for him, and the work was badly done. Only rough notes in his own English remain, and it

is without especial quality. Although his pre-medical education was deplorable, he was not an ignorant man. He could speak Latin. Cicero was the author he most admired, "the great teacher both in thought and language." He frequently quotes Homer, Theocritus, Virgil, Horace, Juvenal, Seneca; and all modern Latin writers were known to him, especially Bacon and Erasmus. He knew the English Bible which was then a new book.

It was from Edinburgh and Leyden the fame of Sydenham first extended to the world. Boerhaave described him as the light of England, an Apollo in the art of medicine, a true pattern of the Hippocratic physician. Haller, a pupil of Boerhaave, who carried Sydenham's method to Germany, discovered him as the beginning of a new epoch in medicine. Van Swieten, a fellow-pupil, bore the seed to Vienna, where it developed into a great clinical school. Arbuthnot in the Harveian oration for 1727, found in him the "aemulus" or emulator of Hippocrates; and more recently the beloved Dr. John Brown describes him as the prince of practical physicians.

This Boerhaave was professor of medicine in Leyden where he succeeded "Sylvius," who had made a vain attempt to reconstruct medicine upon a basis of the new chemistry and the circulation of the blood, losing himself in the technical and the mechanical. Boerhaave lectured five hours a day; his hospital contained only twelve beds, but by Sydenham's method he made of it the medical center of Europe. That knowledge came to him through Edinburgh from Archibald Pitcairne, who for a short time occupied the professor's chair in Leyden, and was the teacher of Boerhaave.

This Archibald Pitcairne was born in Edinburgh in 1652. His ancestor fell at Flodden with his seven sons. The family was continued by a posthumous child. He entered Edinburgh University in 1668, where he graduated Master of Arts in 1671, at the age of nineteen. Then he studied divinity and law. In Paris, where he went for his health, he began the study of medicine but soon returned to Edinburgh, and took up the study of mathematics and medicine. Once more he went to Paris, and graduated doctor of medicine at Rheims. He practised in Edinburgh with wide success, and in 1692 he went to Leyden to occupy a professor's chair. Two of his pupils were Boerhaave and Meade. In 1693 he returned to Edinburgh for his marriage to the daughter of an eminent physician, Sir Archibald Stevenson, from which place he often went as consultant to England and Holland.

Lacking the means of anatomical study, he persuaded the town council to permit him and some of his medical friends to dissect the bodies of paupers in Paul's Work, unclaimed by their relatives. The persuasion was easy, as they agreed to bury the bodies after dissection at their own charge, and to save the town from that expense. To this was added the somewhat dangerous provision, that they were to attend the patients free of cost to the town until they died. This was the origin of the Edinburgh school of medicine.

Anatomy has been the origin of every school of medicine. Human dis-

section is even yet the sovereign method of transforming the average layman into a physician. To this rule neither Hippocrates nor Sydenham is an exception. They did not dissect; but they were men of genius; and genius knows no law. Besides, they did not found schools. The fame of every school, McGill included, is based upon anatomy. It was fixed by Shepherd. I pause to utter a word of respect to his memory. In the modern sense he was not a teacher; but he compelled men to learn by the sheer drudgery of dissection,—dissection not of earthworms, frogs, rats or guinea-pigs, but of the human body. To him the human body, living or dead, was the primary unit in medicine; and in those days the ward-bed and the dissecting table were not very far apart. Indeed, as Sir John Bland-Sutton reminds us, the word κλίνη, from which "clinical" is derived, applies equally to a bed and to a table.

I am well aware that in these days, when a student must be converted into a physiologist, a physicist, a chemist, a biologist, a pharmacologist, and an electrician, there is no time to make a physician of him. That consummation can come only after he has gone out into the world of sickness and suffering, unless indeed his mind is so bemused, his instincts so dulled, his sympathy blunted by the long process of education in those sciences, that he is forever excluded from the art of medicine which was to Hippocrates "the art" of all arts. In that case he is destined for the laboratory, the professor's chair, or the consultant's office. What would have happened to Sydenham, had he been put through this machinery is a problem in infinity which no human intelligence is competent to solve.

Pitcairne like Sydenham insisted upon the strictly scientific method long since enunciated by Bacon: an exact compliance with observation and experience. "Nothing," he affirms, "more hinders physic from being improved than the curiosity of searching into the virtues of medicine; but to enquire whence they have that power is a superfluous amusement, since nature lies concealed. A physician ought therefore to apply himself to discover by experience the effects of medicines and diseases, and not needlessly fatigue himself by enquiring into their causes which are neither possible nor necessary to be known." This is going too far; but we must agree that undergraduates in medicine and practitioners should be debarred from this "superfluous amusement."

Both Sydenham and Pitcairne were convinced that nature lies concealed, and always will be concealed. The more we seek, the further she recedes. To pluck out the heart of her infinite mystery was to them a vain task, and the seeker was sure to go astray. Nature knows no law. The laws of nature were merely our own presuppositions.

Pitcairne was also a poet, a mathematician, a scholar, a collector of books. His library was acquired by Peter the Great of Russia. His monument in Greyfriars churchyard bears an epitaph in testimony of his generosity to scholars. He was the first champion of Harvey. He too failed to win the approval of his colleagues; his plan for dissection was strongly opposed.

His way of life was equally disapproved by the Calvinistic Edinburgh. If we can believe his detractors, he was a frequenter of clubs, public-houses, and taverns. He is reputed to have been drunk twice a day; an unbeliever; much given to profane jests; an atheist; involved in quarrels with the faculty, and suspected by the government.

A curious evidence of his quality is supplied by Richard Meade, his pupil along with Boerhaave at Leyden, afterwards court physician to George II, better known as the discoverer of the *sarcoptes scabiei,* the insect that causes the itch. Pitcairne's son was out in 1715, and was condemned to death. Meade in gratitude to his master interposed and saved his life. He pleaded with Sir Robert Walpole, that if he and the royal family had been cured by his skill, it was due to the instruction he had received from Pitcairne.

The intermediary between Pitcairne and Sydenham was Dr. Andrew Brown. He had read Sydenham's "new and quite contrary method." It so impressed him that he went to London "to settle his tossed thoughts." He spent "some months in his society," and found in him "everything that use to beget in wary and prudent people trust and knowledge." He returned to Edinburgh "as much overjoyed as if he had gained a treasure." He had; he published it to the world in 1691, "a vindicatory schedule concerning the new cure of fevers, first invented by the sagacious Dr. Thomas Sydenham." Pitcairne in the following year carried that treasure to Leyden.

Modern medicine had a resting stage in Edinburgh, whence it issued in two faint streams across the Atlantic to Montreal and Philadelphia. In 1821 the Montreal General Hospital was founded, and from it emanated the McGill medical school. This was the first hospital in America to introduce students into the wards. Here again the old and the new came into conflict. A duel was fought; men had conviction in those days. Five shots were exchanged with ounce bullets. One protagonist was shot through the chest; the other had his right arm shattered. Both recovered, the one by the old treatment, the other by the new, so their comparative merit was left undecided. The four founders were Edinburgh men.

When the College of Physicians of Philadelphia was founded in 1787, four of the eleven senior fellows had graduated from Edinburgh, and four others had studied there, "children of Edinburgh and grandchildren of Leyden," as Weir Mitchell said. There is in the Frick library a collection of 126 theses, presented by Sir William Osler, written by American students in Edinburgh between the years 1760 and 1813. Some of them bear the names of Morgan, who founded the first American medical school in the University of Pennsylvania in 1763; of Shippen, Kuhn, Logan, Rush, and Lee. The first clinical lecture was given by Thomas Bond in 1766, on the advantages of clinical instruction. He took the precaution of reading it in advance to the board of managers who inscribed it in their minutes. To complete the record, Osler in 1885 went to Philadelphia, bearing with him what he had learned at McGill; and so these two streams of modern medicine were joined.

If I stopped at this point, I should be a mere historian repeating what you already know, or can read in books. Sydenham's little writings are at your hand in Latin and English, published by the old Sydenham Society. Everything germane to the subject has been collected by Dr. F. Picard, and by J. F. Payne in 1900. From this material, small though complete as it is, many charming essays have been drawn, none more charming than that by H. H. Bashford in his Harley Street Calendar.

But history is the master to whom we all must go. If now we are convinced that Sydenham has achieved a world mastery in medicine we might do well to enquire how close we come to his mind, or how far we have departed from it. For the moment I shall content myself with one aspect—medical education—a subject upon which Sydenham expressed himself without reserve. We must not rely too implicitly upon even his authority for he had no experience in the public teaching of students; he never had a hospital appointment, never occupied a professor's chair. He had, however, some private pupils, one of whom was Dr. Dover whose powder yet bears his name. His own instruction at Oxford was scanty; he never entered a laboratory; never walked through a ward; there were no wards to walk in. He mentions Aristotle only once, Galen three times, Celsus not at all.

If a young man were to ask you by what means he should achieve a medical education, you would feel compelled to offer him the curriculum for the first two years. They are much the same; they represent the sum of our wisdom. In one recently under my hand, the first year is assigned to physiology, anatomy, histology, and organogen; although if the aspirant asked me what "organogen" meant, I should be obliged to confess that I do not know; unless indeed it is derived from the Greek word ὄναργος through the Latin *onager*. In the second year, biochemistry and pharmacology are added; with lectures on public health and the history of medicine. It is not on record that the neophyte comes into the remotest contact with a sick human being for two years. The London schools are within the hospitals, and students from curiosity or boredom wander with new interest and profit into the wards. The French go to the other extreme, and assign clinical duties to a student on the first day of his entrance.

This very question of medical education was put to Sydenham by Hans Sloane, who afterwards achieved the highest professional and social honors, and is yet remembered as the founder of the British Museum. The young man modestly suggested that he might take a course in anatomy and botany. "This is all very fine," said Sydenham; "but it won't do. Anatomy, botany,—Nonsense, Sir. I know an old woman in Covent Garden who understands botany better; and as for anatomy, my butcher can dissect a joint full as well. No, young man; all this is stuff: you must go to the bedside; it is there alone you can learn disease." Rather than go abroad to study botany, he recommended this earnest seeker to drown him-

self in a pond that was commonly used for that purpose. The frightful thing is that he may have been right.

Sydenham was a physician, an artist, a practitioner; he thought that enough for any one person. He was not an ultimate scientist, not a botanist, anatomist, or physiologist. These were separate trades; they concerned him indirectly or not at all; they destroyed in the practiser the quality of physician. He had a passion for curing the sick, which expelled all other interests.

He does not seem to have heard of Harvey or the circulation of the blood, which was then a discovery 40 years old. Osler goes further when he writes: " There was nothing in Harvey's discovery which could be converted immediately into practical benefit, nothing that even the Sydenham of his day could take hold of and use." He knew nothing of Malpighi's discovery of the arterioles twenty years earlier. Indeed he averred that not even the microscope could disclose them. These to him were explanations, and he kept his mind upon the majesty of open facts. He gave to medicine a method which was more valuable than detailed discovery; he brought canonical authority to an end. But, strange to say, this method was soon to be extended into those fields of science of which he professed himself negligent or ignorant. Boerhaave applied that method to anatomy, physiology, and the microscope. Haller bore it with him to Göttingen, and developed physiology into a natural science; Morgagni in morbid anatomy was " the counterpart of Sydenham."

If Sydenham in his mature age began to practise in any American city, he would be put in gaol; if he applied with his poor preliminary qualification to study medicine in the first year of any medical school, he would be put in the asylum, along with Shakespeare, if he were found wandering about, after he had applied to a high-school as an instructor in English composition. We in Canada have been in the habit of blaming the United States for our established curricula. Forty per cent of our medical students at McGill are Americans; they help to pay our salaries, although they do profit to the extent of 600 dollars a year from our pious endowments.

In times gone by, Canadian graduates went freely to the United States to practise. We felt obliged to conform with the regulations of the various State boards; we still feel obliged in a measure to meet the legal needs of our American students. Now the border is more strictly closed. If an American physician comes to us, he comes on his own record since graduation. No one thinks of asking how or where Penfield, or Cone, or Stehle studied. If now our curricula are too abstract, the fault is our own. We have to deal only with the various provincial boards. The eye of the legislatures is upon them and upon us; and they are swift to act. One Canadian provincial board is much more rigid than any similar body in the United States. The final Report of the Commission on Medical Education, issued last month, discloses that all State regulations are completely relaxed, and the schools are now free. The head of one Board writes, that licensing

examinations, " as such," that is, apart from the candidate's school record, are worthless. Sydenham would sanction the profound sanity of this Report.

Let us now, in conclusion, try to discover if Sydenham's practice has any lesson for us. When he came upon the scene, practice had become so scientific that the most scientific physician did not even look upon his patients. In Paris their excretion was carried to him in an earthen vessel by a servant. By inspection of that alone he made a diagnosis, and sent the proper remedy. To be " elaborately curled " was a favorable sign. A similar practice prevailed in Scotland, if we can believe the panegyric of Robert Burns upon Doctor Hornbook, except that the mode of conveyance was upon a " kail-blade," that is, a cabbage leaf.

We in our time have departed still further from reality, when we substitute a photograph for the thing itself. The older surgeons were content to diagnose a broken leg if the end of the bone protruded through the skin. Now, we must have a picture. The fault is not wholly with the surgeon. The poorest patient is so hedged about with insurance that the surgeon must provide himself with the evidence the court may require. Nothing lies like the camera, especially when the deeper structures are involved. By a judicious use of the camera, a fish may be made to appear as long as the man who caught it. In hospitals, given over mainly to chronic and convalescent cases, an expert photographer comes once a week to " read " the pictures that have been made in the interval by the " technicians." He makes the diagnosis and suggests the treatment, although he has never seen a patient *qua* patient since the day he acquired his degree.

If Sydenham were alive today, and came into a modern hospital, he would be for the moment bewildered. He would have to teach himself that the field of medicine has been immensely widened, and cannot even be surveyed by a single mind. He would see acute conditions diagnosed at a glance, and swift treatment applied. But he would see obscure cases which had baffled practitioners as earnest as himself. He would discover, to his joy, that the chief physician was so scientifically conscientious that he would not make a diagnosis, still less prescribe anything more than a palliative treatment until he had before him all the reports of his various expert assistants. By the time the file was complete, the patient might have left the hospital alive or dead. If living, he might take his file with him, to display with the interest he had in his family album. But the visitor would recognize in that physician a brother to himself,—with this reserve, that the patient be not lost in the problem, or the physician in the abstract scientist. The world may be a stage: it is not a hospital, as the young man will discover when he begins to practise, deprived of apparatus, and compelled to rely upon his own natural senses.

Sydenham would be astonished at the magnificence of the modern hospital, and wonder if practice could not be reduced to a " greater easiness," thinking of the days when he fought his troopers and doctored them,

too, as indeed the soldiers in the recent war were adequately treated in aid-post, dressing station, field ambulance, and in rest stations for their convalescence. He would ask, as many are now asking, who bears the expense of three dollars a day for each public patient, described in his time as a pauper.

Unless the hospitals for public patients curb their scientific curiosity and return to the simple practice of Sydenham, their task will be taken away from them and given to another. Science, too, is governed by economic law. Even private patients are beginning to discover, as Sydenham did, that they can get well without becoming victims of the scientific ritual. Any patient who lives long enough will get well. Life is not now so desirable as it used to be. To die in peace is better than a few months of added misery.

Nature may be expelled; insensibly she returns. Happily, the tide of practice is now turning again to the bedside. The voice of Sydenham is being heard anew. To a patient clamoring for drugs and operation David MacKenzie said: "The quickest and cheapest way to recovery is lying in that bed." Sydenham said to Locke: "You will best cherish yourself by keeping to bed; it will contribute more to your relief than can be imagined." Dean Martin instructs his students that the educated hand and ear will tell the average physician enough, and all he can understand, towards treating a patient with heart disease. Electrical machinery is for the expert; he alone can tell if the fibrillations that appear upon the photograph are really in the heart or are due to extra-cardial electrical currents induced by a nearby radio or a vacuum cleaner in the hands of a ward-maid. John Meakins informs his students that the one question that really interests a patient is how soon he can resume his usual employment. Francis W. Peabody, six years ago, expounded to the students of Harvard the complete care of the patient.

Sydenham was a Puritan; he believed that scientific truth came as a revelation from heaven; or as we would say by an act of intuition in a creative mind. Experiments were of no avail, unless there was a mind to interpret them and discern the end to which they led. All else was mere research, searching for the already seen, or an aimless wandering in the mazes of nature. He made no objection to these experimenters. They might be as abstract and finical as they liked; he merely insisted that they know what they were trying to do, and above all keep out of the field of practical medicine, and not lead the minds of the young away from the bedside. There is a lesson in that for the laboratories.

Fame enough has come to Sydenham; but he had "long since weighed in a nice and scrupulous balance, whether it were better to serve men or be praised by them."

EDITORIALS

THE HEART AND THE SURGEON

IT SHOULD be of particular interest to physicians that some of the most important progress in the treatment of heart disease lies in the realm of surgery. It is very necessary for the physician to know what the surgeon can do and when to call him in.

Three totally different types of surgical procedure, each designed to relieve the sufferer from heart disease by altering certain of his physiologic processes, may be mentioned.

In the first place we have the nerve blocking procedures for painful afflictions such as angina pectoris. These, whether they be alcohol block, nerve section, or ganglionectomy, all serve merely to abolish pain by interrupting the arc over which the pain is referred. They cannot materially prolong life nor stay the progress of disease. Conceivably they may shorten life by removing the danger signal which pain may provide. However, because their use is commonly restricted to those patients whose misery is so great that life is not worth living this theoretical objection is of no moment. Since Jonnesco[1] first introduced procedures of this sort in 1916 much knowledge of the exact nature of the pathways has been gained with the result that the attack now should be made no longer upon the upper and middle cervical sympathetic ganglia, but instead upon the inferior cervical and upper dorsal ganglia or the posterior roots of the upper dorsal spinal nerves.[2]

Another category of cardiac operation is that of decortication or decompression of the heart. A pump enclosed in a rigid sack which does not permit it fully to relax obviously is handicapped in the quantity of pumping it can do. The heart may fall into this predicament when the pericardium is diseased as in constricting mediastino-pericarditis, of which the syndrome of Pick is an advanced stage. Also dense adhesions may so firmly anchor the heart to the unyielding chest wall that its action is grossly disturbed. In this event it may be more its contraction than its filling which is hindered. In either case the surgeon may be able to set free the struggling organ from restraint[3] and relieve the patient of the symptoms that interference with heart action produced. The syndrome of Pick has been produced by the injection into the pericardial sack of substances which induce an adhesive process. This experimental syndrome has then been relieved by decortication of the heart.[4] In somewhat similar fashion very huge hearts may

[1] JONNESCO, T.: Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique, Bull. Acad. de Médicine, Paris, 1920, lxxxiv, 93.

[2] WHITE, J. C., GARREY, W. E., and ATKINS, J. A.: Cardiac innervation, experimental and clinical studies, Arch. of Surg., 1933, xxvi, 765.

[3] CHURCHILL, E. D.: Decortication of the heart (Delorme) for adhesive pericarditis, Arch. of Surg., 1929, xix (Part II), 1457–1469.

[4] BECK, C. S., and GRISWOLD, R. A.: Pericardiectomy in the treatment of the Pick syndrome, Arch. of Surg., 1930, xxi, 1064.

suffer embarrassment from the very fact that the thorax itself becomes relatively confining. In such cases the substitution of a flexible for a rigid precordium through rib resection (decompression) may give greater ease of function.[5]

Endocardial operations have been tried, chiefly to relieve stenoses. They have not given results which are at all encouraging. Moreover while nerve block and decortication have in certain instances been brilliantly successful the cases in which they are indicated are far from plentiful. However, there is a totally different type of operation for heart disease which has been introduced quite recently by Blumgart and his collaborators,[6] which bids fair to have a far wider application. This, like the other type, is based upon simple physiological principles.

The heart which is overburdened may be helped if its burden is reduced. The insufficiency of any organ may result on the one hand from an excessive demand placed upon it by the body as a whole, or on the other by a reduction in capacity for work of the organ itself. The two may be combined. The efficiency of organs in general depends upon the relation of *demand for* function and *supply of* function. The work performed by the heart is a function of mass of blood moved and resistance encountered. Mass of blood moved depends, primarily, upon the call for oxygen by the tissues, that is to say, upon metabolism.

The Boston investigators argued that reduction in metabolic rate by thyroidectomy ought to help certain cardiac cripples by reducing the work their hearts were called upon to do. If the heart's capacity cannot be increased the patients still may be benefited by making their hearts work less. At the lower level the heart may actually become competent. So they argued and since they had the courage of their convictions, so they carried on. In eleven of thirteen cases the results in the first few months seem brilliantly successful.

Of course it has long been known that the thyrocardiac is benefited by partial thyroidectomy. In the thyrotoxic person partial thyroidectomy usually permanently lowers metabolic rate. This is not so in persons with normal thyroid glands. In them the whole thyroid must be removed. If any gland tissue is left it soon hypertrophies and no permanent drop in metabolic rate is secured. The development of a safe technic for absolutely total extirpation of the normal thyroid gland is the contribution of Dr.

[5] Morison, A.: Thoracostomy in heart disease, Lancet, 1908, 38.
Lenormant, Ch., and D'Aubigne, R. M.: La thoracectomie précordiale dans les symphyses et certaines hypertrophies cardiaques, J. de chir., 1928, xxxi, 161–175.

[6] Blumgart, H. L., Levine, S. A., and Berlin, D. D.: The therapeutic effect of thyroidectomy on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity, Arch. Int. Med., 1933.
Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D.: The therapeutic effect of total ablation of the thyroid on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity. III. Early results in various types of cardiovascular disease and coincident pathological states, Arch. Int. Med. (In Press).

Berlin, the surgeon of the Boston group.[7] It is a very special technic, with considerable risk, a very different business from ordinary subtotal thyroidectomy for goiter. It should be undertaken only by surgeons who have given it special study; by such, however, it may be successfully carried out. The myxedema which will soon result in cases so treated can be perfectly controlled. Patients with full-blown, spontaneous myxedema usually have metabolic rates of —40 or below. They seldom show much clinical evidence of myxedema when their rates are not lower than —25. By the use of small doses of thyroid it will be quite easy to run these thyroidectomized cardiac patients at metabolic rates in the neighborhood of —25 which will avoid gross myxedema, yet effect a great saving to the heart.

Another aspect of the matter is that of coronary flow. The principle of demand and supply may be applied to coronary flow no less than to total cardiac work. It has long been a common clinical experience to find that certain patients with myxedema develop angina pectoris when given thyroid. Angina may be taken to be the symptom of relative insufficiency of coronary flow. The myxedema patient's coronaries may be sufficiently capacious for his low rate of blood flow and consequent light cardiac work. When his general metabolism and his heart metabolism are stepped up by the thyroid he receives, then his coronaries may become unable to meet their task. Blumgart and his collaborators, recognizing this, argued that total thyroidectomy in ordinary cases of angina pectoris might, by lowering metabolic rate and diminishing the quantity of blood the coronaries are required to let pass, bring about a state of relative coronary competence. Again in actual experience their thought seems to have been proved sound. Indeed, it seems likely that total thyroidectomy may turn out to be a far better procedure for angina pectoris than any form of interruption of the nervous arc. It may not only prevent pain but also prolong life.

Progress of this kind indicates the necessity for a broadly physiologic point of view. In the field of cardio-vascular disease the hemodynamic aspects must not be lost from sight in the welter of a mass of electrocardiographic and statistical facts. What we want to know chiefly about a pump is how well it can pump, and the patient is keener to have us do something which will prolong and improve the pumping of his heart than he is to have us tell him with some nice degree of accuracy when it will cease.

J. H. MEANS

SYPHILITIC AORTITIS

AMONG the lesions of late syphilis, syphilitic aortitis by virtue of its serious complications ranks high as a cause of fatalities. It is estimated that cases of cardiovascular syphilis constitute over one-tenth of all cases of organic heart disease. Moore believes that there may be as many as

[7] BERLIN, D. D.: The therapeutic effect of complete thyroidectomy on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity. II. Operative technic, Am. Jr. Surg. (In press.)

20,000 deaths a year from this cause in the United States. Of these a certain proportion are due to aneurysm, but the majority result from heart failure. For the most part it is not the aortitis which causes heart failure but the extension of the aortitis to the aortic valves with resultant aortic insufficiency, or the encroachment of the aortic lesions upon the openings of the coronaries bringing about stenosis or occlusion of these orifices.

It is still a subject of discussion whether a true syphilitic myocarditis occurs in association with specific aortitis or whether the pathological changes in the myocardium are explainable as a result of the mechanical stresses of the valvular lesion, the ischemia due to coronary stenosis at the ostia, or in many instances to the presence in the same patient of coronary arteriosclerosis. The inability of most pathologists to demonstrate spirochetes in the heart weighs somewhat against the specific nature of the lesions. In any case there is little evidence that a diffuse syphilitic myocarditis ever occurs in the absence of specific aortitis so that aortitis in nearly all cases may safely be assumed to constitute the primary syphilitic focus from which all lesions which cause heart failure later develop.

In the reports based on cases in which, irrespective of the cause of death, autopsy has demonstrated the presence of late syphilis it is shown that syphilitic aortitis is the commonest tertiary lesion with an incidence of approximately 80 per cent. In living patients, however, in whom the diagnosis of late syphilis has been made according to clinical and laboratory criteria, syphilitic aortitis is much less frequently diagnosed. In the analysis of a group of 6,420 ambulatory cases of late syphilis, Turner found evidence of cardiovascular syphilis in only 10.1 per cent; the diagnosis of uncomplicated aortitis was made in 5.1 per cent.

It is apparent that in known syphilitics the presence of syphilitic aortitis is frequently overlooked by our present methods of diagnosis and that moreover we are not able to utilize to the fullest the presence of this lesion as a means of diagnosing syphilis in cases presenting no other stigmata of this disease.

The diagnosis of syphilitic aortitis today is most accurate at a stage of the disease when the making of this diagnosis is least useful to the patient. When aneurysm, aortic insufficiency or symptoms of coronary stenosis are found we are frequently able to conclude that there is present an underlying aortic syphilis; but the opportunity for effective treatment in such cases has already passed. Treatment at best will only delay the inevitable end. To the individual patient at this stage, judicious treatment has much to offer, but no successful attack upon the mortality rate from cardiovascular syphilis can be initiated so late.

The diagnosis of uncomplicated syphilitic aortitis may be made with some certainty in a rather limited number of cases. In cases of known syphilis in which the ascending portion and the arch of the aorta are dilated, without other known cause such as hypertension and arteriosclerosis, the diagnosis of syphilitic aortitis is justified. The physical signs which sug-

gest such a dilatation, increased retromanubrial dulness, abnormal pulsation in the jugular fossa, drum-like aortic second sound are unfortunately easily overlooked perhaps because in some cases their significance is not appreciated and special attention is not given to their detection. Roentgenology may be of great assistance but here again routine procedures will often fail where more careful fluoroscopy from various angles or the use of oblique teleroentgenography would elicit evidence of dilatation.

A higher "index of suspicion" among physicians and consequent increased clinical alertness would no doubt add appreciably to the number of cases in which the diagnosis of uncomplicated syphilitic aortitis was arrived at by the determination of the presence of aortic dilatation. At best, however, this method of diagnosis is limited in its application. In the first place in patients over forty-five widening of the aortic contour from other causes than syphilis is sufficiently frequent and difficult to differentiate to greatly subtract from the specificity of this finding. In the fifties syphilis of the aorta is almost always combined with arteriosclerosis. In the second place detectable dilatation of the aorta probably occurs only in cases in which the involvement is extensive. It is evident indeed from the study of pathological specimens that not all cases even of extensive aortitis are accompanied by dilatation. It has appeared to be more common in those cases complicated by an aortic insufficiency or accompanied by hypertension. At any rate aortic dilatation is surely often absent in those frequent cases in which the aortitis is limited to a small area in the suprasigmoid region of the aortic wall. The danger of involvement of the coronary orifices or of the aortic valves from such a small focus is unfortunately greater because of propinquity, than it is from a more extensive process at a higher level.

The symptomatology at present ascribed to syphilitic aortitis is of very slight diagnostic help. It is for the most part not the product of a careful comparison of clinical observations with pathological findings. It has come down to us from a less critical day and seems compounded of symptoms attributable as much to concurrent coronary ostial stenosis, aortic insufficiency, and even aneurysm as to the aortitis *per se*. There is no doubt, however, that aortitis produces symptoms and it seems very possible that a more intensive clinical and pathological comparison may give us a clinical picture of diagnostic value.

The need for further diagnostic aid in the early detection of aortic syphilis is a very real one. The finding of any syphilitic lesion may unravel many other diagnostic tangles; but especially is it important to discover a lesion so apt to attack vital structures. It now appears probable though not proven that this aortic lesion in its early stages may be controllable by treatment. It seems also established that it is most safely treated not by routine measures but by a more carefully graded use of anti-syphilitic remedies. An improvement in our present methods of diagnosis of syphilitic aortitis will therefore constitute a major contribution to internal medicine.

REVIEWS

Clinical Diagnosis: Physical and Differential. By NEUTON S. STERN, A.B., M.D., Harvard; Associate Professor of Medicine, University of Tennessee School of Medicine, Memphis. xvi + 364 pages. The Macmillan Company, New York, 1933. Price, $3.50.

Dr. Stern has written a textbook that in the reviewer's opinion is most timely. Most textbooks on physical diagnosis either confine themselves solely to the chest organs or are so large and cumbersome that anything like a complete reading constitutes something of an ordeal.

In this book, however, Dr. Stern combines completeness with brevity. He crowds an astonishing amount of information into something less than four hundred pages. His description of the mechanisms involved in physical diagnosis is simple, direct and understandable. His outline of laboratory technic is adequate to the requirements of most practitioners and students. His section on the interpretation of symptoms is admirable. He admits with pride that his section on case history teaching has been borrowed from Richard C. Cabot. He emphasizes over and over again the value of thoroughness and completeness. The American Heart and Tuberculosis Association's standards of measurements and classification have been adopted, which the reviewer considers a valuable feature.

One hesitates to criticize in any way a textbook with which one is in such marked agreement, but the reviewer feels that in discussing history writing, Dr. Stern might perhaps have laid greater emphasis on the past history and have drawn a clearer distinction between the events of the past history and the present illness. A few illustrations would also have enhanced the value of the book.

However, the whole book is so useful and so clear that it deserves to achieve immediate acceptance as a standard text for undergraduate teaching. It cannot fail to be useful to graduate clinicians who wish fundamental information in an accessible form.

T. C. W.

Calcium Metabolism and Calcium Therapy. By ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College, with a foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., Late Professor Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Ed. II. xii + 252 pages; 20 × 14 cm. Lea and Febiger, Philadelphia, Pa. 1933. Price, $2.50.

The contents of this volume are divided into three general headings: Normal Calcium Metabolism, Abnormal Calcium Metabolism and Calcium Therapy.

In the five chapters which compose the first part of the book such subjects as Calcium Requirement, Calcium Excretion, Blood Calcium and other related topics are discussed. Of special interest in this section is the discussion of the calcium level of the plasma as it is related to the parathyroid hormone and vitamin D. Besides these factors which exercise an important control over the calcium balance of the plasma, the acid-base balance is emphasized. The optimum pH in vitro for calcification is 7.25 to 7.30. Slight calcification occurs at pH 7.00 to 7.10 and no calcification occurs in solutions more acid than pH 7.00. In the form of a recapitulation, the author states that there are five factors which may increase the excretion of calcium, causing a negative calcium balance, and a decalcification of bone: (1) Thyroid Extract, (2) Parathyroid Extract, (3) Vitamin D Deficiency, (4) Excess of Phosphorus, (5) Acidosis.

There are two chapters in Part Two dealing with the abnormalities of calcium metabolism. The hypocalcemias which accompany many forms of disease are treated

from a theoretical and practical standpoint. The author is especially thorough in his discussions of the influence of various diseases on the character of blood calcium. This is discussed from the point of view of modern physicochemical concepts.

Part Three treats of calcium therapy in its various ramifications. It is gratifying to observe that the author approaches this problem logically, viz., having considered the physicochemical features of blood calcium, the pharmacological are developed next and finally the therapeutics of various calcium salts. The effects of giving calcium salts by the various avenues of administration are compared. After the oral administration of calcium salts lactose is recommended as it enhances the absorption of calcium by increasing intestinal acidity through lactic acid fermentation. The rôle of the active parathyroid extract, prepared by Collip, is discussed in its relationship to calcium therapy. In the author's opinion the discovery of this extract has immeasurably enriched the possibilities of calcium therapy.

The treatise is well written and practically free from typographical errors. The volume fulfills the purpose for which it is intended, namely, to familiarize the clinician with certain aspects of calcium metabolism, and to aid in the establishment of calcium therapy upon a rational basis with full realization of its value and limitations.

J. C. K., Jr.

The Duodenum—Its Structure and Function, Its Diseases and Their Medical and Surgical Treatment. By Edward L. Kellogg, M.D., F.A.C.S. 882 pages. Paul B. Hoeber, Inc., New York, 1933. Price, $10.00.

This work true to its substantial title is one of considerable scope and no little value. The author has collected under one cover an enormous amount of data of which the preponderant amount is well selected and correctly interpreted. Naturally in a work of this size there are bound to be subjects on which points of view will differ markedly. The work may be roughly divided into sections dealing with (1) anatomy and physiology; (2) diagnostic technic; (3) a description of the various diseases and disorders that are found in the organ and the indications for their medical and surgical treatment; and (4) a long chapter on surgical procedures.

It is in the third section that the major part of the book's value is to be found. Herein are tabulated in meticulous detail the age, incidence of occurrence, X-ray findings, congenital variations, case histories, etc., appertaining to such subjects as Duodenitis, Abnormalities of Shape and Position, Diverticulosis of the Duodenum, Internal and External Fistulae, Duodenal Hernia, Duodenal Obstructions Caused by Annular Pancreas, Duodenal Ulcer, etc.

The chapter on X-Ray Diagnosis is written by A. Judson Quimby, M.D., and that on Duodenal Parasites by Bailey K. Ashford, M.D. The latter is particularly well done.

As a reference book on the incidence, details and statistics of all types of duodenal abnormalities this volume is particularly recommended.

L. M.

Peptic Ulcer. By Jacob Buckstein, M.D. Volume Ten of Annals of Roentgenology—A Series of Monographic Atlases. Edited by James T. Case, M.D. 444 pages. Paul B. Hoeber, Inc., New York, 1933. Price, $12.00.

To the series of Monographic Atlases in Roentgenology has been added the Second Edition of the volume, *Peptic Ulcer.* In it the author presents a series of common and rare roentgenological views of gastric, duodenal, and post-operative gastrojejunal and jejunal ulcers. Interesting historical sketches on the development of radiological technic in each one of these conditions are followed by a large number of films. A case record, short and concise, is given with each photograph.

In addition, valuable, common sense reflections on conditions in which the differential diagnosis is difficult are given, in connection with well chosen illustrations.

The work is well planned, well printed and bound. It is well worth a place on one's shelves as a reference volume in peptic ulcer roentgenology.

L. M.

Physical Chemistry of Living Tissues and Life Processes. By R. BEUTNER, M.D., Ph.D., Professor of Pharmacology, School of Medicine, University of Louisville. Ed. I. ix + 337 pages; 23 × 15 cm. The Williams and Wilkins Company, Baltimore, Md. 1933. Price, $5.00.

To bridge the gap between inanimate and living matter is the time-honored problem of the basic sciences. Physical chemistry is a powerful tool in the hands of the biologist to shed light upon this fundamental problem. In a masterly manner the author has attempted to elucidate the physical and biological observations which tend to show an analogy between the behavior of inanimate systems and biological processes.

The writer has avoided the mathematical formulae concomitant with physicochemical developments in order to keep the book available to the average student of medicine. However, fortunately for those who are interested in the mathematical development of the field, a mathematical treatment of certain theories has been included in the appendix.

The approach to the problem is divided under three separate headings. First, Membranes, Osmosis and Related Forces are considered; second, Life Processes Related to Crystallization or Owing to Surface Forces are dealt with; and third, Electrical Currents in Tissues and Their Relation to Life Processes are treated. These three main divisions of the book are followed by a chapter on Future Possibilities of Development which deals particularly with Artificial Parthenogenesis.

The reviewer is particularly impressed by the scholarly and philosophic approach to the entire problem which is embodied in the introduction dealing with Life as a Scientific Problem.

Of particular interest to the clinician is the section of the book in which the physicochemical aspects of edema and nephritis are described. Pharmacologists and physiologists will find the Meltzer and Auer's magnesium-calcium antagonism and related phenomena particularly well described.

The style of the author is clear and concise. His statements are in most instances accurate reproductions of original work or careful deductions therefrom. On page 27, it would have been well to point out that cryoscopic measurements involving molecular weight determinations are conducted on the basis of gram-molecular weights in 1000 grams of the solvent and not on the basis of molar solutions. Considering the nice differences between the pH of arterial and venous blood, it is regrettable that nothing is mentioned in this connection on page 74. In the explanation of reversible emulsions, no mention is made of Harkin's orientation theory which provides a brilliant hypothesis for the phenomenon in question.

In its entirety, the book fulfills the purpose of the author as previously set forth and points out with convincing assuredness that, "Life in all of its complexity seems to be no more than one of the innumerable properties of the compounds of carbon."

J. C. K., JR.

The Medical Secretary. By MINNIE GENEVIEVE MORSE, Member, Board of Registration, Association of Record Librarians of North America. viii + 162 pages; 11 × 17 cm. The Macmillan Company, New York, 1933. Price, $1.50.

Although this book is written primarily for the secretary lacking medical training and the nurse to whom secretarial work is new, it will also be helpful and interesting

to secretaries already in the medical field. There are nine chapters: I. Qualifications for Medical Secretarial Work, in which stenography and typewriting, medical terminology, correct English, foreign languages, indexing and filing, history-taking, manuscript preparation, mimeographing and multigraphing, handwriting, and miscellaneous office responsibilities are considered; II. The Personality of the Medical Secretary, which stresses the importance of dress, manners, tact, initiative and trustworthiness; III. Office and Patient, which discusses in connection with the former the reception room, the consulting room, the treatment room and the sterilization of equipment, and in connection with the latter the duties of the nurse or nurse-secretary in the examination and treatment of patients; IV. Medical Correspondence, Bills, and Reports, most of which will be merely a review for the person with previous secretarial experience; V. Case Records, which should give the unfamiliar an idea of what a hospital case chart and a case history include; VI. Medical Indexing and Filing; VII. Medical Research, in which "the simplest form of research," the making of a bibliography, is handled rather inadequately inasmuch as, while it gives several styles of listing references, it contains no information as to how to go about looking up references; VIII. The Preparation of Medical Manuscripts, which includes a useful group of signs used in correcting proof; and IX. Medical Terminology, with a list of medical abbreviations, prefixes and suffixes, and an outline of medical terms compiled "by dividing the body into regions and systems, arranged in alphabetical order, associating with the names of the organs and tissues in each division the names of the principal diseases to which they are liable and the principle operations which may be performed upon them." A bibliography of fifteen books concludes the volume.

M. F. L.

COLLEGE NEWS NOTES

In view of the removal of the Editorial Office of the ANNALS OF INTERNAL MEDICINE to Baltimore, it was found necessary to sever the long and cordial relations which have existed between this journal and the Ann Arbor Press and to place the printing of the ANNALS with a firm in closer proximity to the Editor. Beginning with the present number, the ANNALS will be printed and issued by the Lancaster Press of Lancaster, Pennsylvania. The extensive experience of this firm in printing scientific journals assures us of the continuance of the typographical standards of our journal. With this new volume, certain changes in format have been introduced which the Editor hopes will meet with the approval of our readers.

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill.—1 book, "Asthma, Hay Fever and Related Disorders";
Dr. A. C. Clasen (Fellow), Kansas City, Mo.—2 reprints;
Dr. Henry A. Rafsky (Fellow), New York, N. Y.—3 reprints;
Dr. Walter Clarke (Associate), New York, N. Y.—2 reprints;
Dr. August A. Werner (Associate), St. Louis, Mo.—4 reprints.

More than half of the Fellows and Associates of the American College of Physicians residing in the State of North Carolina assembled at a special luncheon at the Sir Walter Hotel, Raleigh, N. C., on April 19th. These round-table luncheons have been held previously by the North Carolina Fellows and are kept entirely to a social plane. Dr. William Gerry Morgan, Secretary General of the College, Washington, D. C., was a guest of honor and spoke informally about the work and activities of the College. Dr. Charles H. Cocke, Asheville, Governor of the College for North Carolina, delivered an address, urging members to maintain the keen interest in the College that they have shown heretofore, and leading a discussion on various aspects of College activities.

Dr. Carl V. Weller (Fellow), Director of the Pathological Laboratories, University of Michigan, Ann Arbor, Mich., spoke before the American Society for Experimental Pathology in Cincinnati, Ohio, during April on the subject of "The Pathogenesis of Trichinous Myocarditis." Dr. Weller was elected President of that Society for the ensuing year.

Dr. Milton A. Bridges (Fellow), New York City, in collaboration with Ruth L. Gallup, is author of a new book on "Dietetics for the Clinician," recently published by Lea and Febiger of Philadelphia.

Major Edgar Erskine Hume (Fellow), Medical Corps, U. S. Army, Librarian of the Army Medical Library, Washington, D. C., has been elected a Fellow of the Royal Society of Edinburgh.

Dr. Stewart R. Roberts (Fellow), Atlanta, Ga., was recently elected President of the American Heart Association.

Dr. James A. Lyon (Fellow), Washington, D. C., is President of the Washington Heart Association for the current year.

Dr. F. O. Mahony (Fellow), El Dorado, Ark., was chosen President-Elect of the Arkansas State Medical Society at its annual meeting at Hot Springs, May 2nd, 3rd and 4th.

Dr. James Z. Naurison (Fellow), Springfield, Mass., has been elected President of the Hampden District Medical Society for 1933–1934.

Dr. C. W. Strickler (Fellow), Atlanta, Ga., has been elected President of the Staff of Grady Hospital, Atlanta.

At the recent annual meeting of the Medical Society of the State of North Carolina, Dr. I. H. Manning (Fellow), Dean of the University of North Carolina Medical School, succeeded to the Presidency, while Dr. P. P. McCain (Fellow), Sanatorium, was made President-Elect and Dr. R. L. Felts (Fellow), Durham, First Vice-President.

Metabolic Disorders will be the theme of the 1933 Graduate Fortnight of the New York Academy of Medicine. Two weeks of intensive study from October 23rd to November 3rd, inclusive, will be devoted to this important branch of medical science. The theoretical, physiologic and pathologic phases of Metabolism, as well as of certain of the associated endocrinologic problems, will be treated in a series of round-table discussions and clinical demonstrations. Among the speakers are the following Fellows of the College:

Dr. Walter W. Palmer, New York City
Dr. Emanuel Libman, New York City
Dr. Priscilla White, Boston.

Dr. Fred G. Holmes (Fellow), Phoenix, Ariz., was named President-Elect of the Arizona State Medical Association at its annual meeting in April.

Dr. Arthur C. Christie (Fellow), Washington, D. C., and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., were guest speakers at the annual meeting of the California Medical Association in April.

Dr. Joseph D. Applewhite (Fellow), Macon, Ga., was elected a Vice-President of the Medical Association of Georgia at its recent annual meeting in Macon.

Dr. Ernest E. Irons (Fellow), Dean of Rush Medical College, Chicago, has been appointed Chairman of the Department of Medicine to succeed Dr. George F. Dick.

Dr. Allen K. Krause (Fellow), Tucson, Ariz., delivered the annual Trudeau Lecture at the joint meeting of the St. Louis Medical Society and the St. Louis Trudeau Club during April, his subject being "The Principles of Activity in Pulmonary Tuberculosis."

Dr. William E. Nesbit (Fellow), San Antonio, Texas, was elected President of the Texas Club of Internists at its spring meeting in Fort Worth during March.

Dr. Allen K. Krause (Fellow), Tucson, Ariz., was the guest speaker.

Dr. Julius H. Hess (Fellow) and Dr. Robert A. Black (Fellow), both of Chicago, are among those selected to organize groups of teachers to conduct a one-day lecture course in Pediatrics in eleven districts of Illinois, under the auspices of the American Academy of Pediatrics and the Educational Committee of the Illinois State Medical Society.

Dr. James B. Herrick (Fellow), Chicago, Ill., was elected President of the American Association of the History of Medicine at its annual meeting in Washington during May. Dr. Herrick succeeds Dr. Gerald B. Webb (Fellow), of Colorado Springs, Colo.

Dr. William S. Middleton (Fellow), Madison, Wis., was elected a Vice-President, and Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., Secretary.

Dr. Francis G. Blake (Fellow), Sterling Professor of Medicine in the Yale University School of Medicine, has been appointed Chairman of the Division of Medical Sciences of the National Research Council.

Dr. Wilmarth B. Walker (Associate), Cornwall, Conn., was elected Secretary of the Litchfield County Medical Society at its 169th annual meeting during April.

Dr. Edward B. Vedder (Fellow) was recently appointed full-time Professor of Experimental Medicine and Executive Officer of the Department of Pathology and Experimental Medicine of the George Washington University School of Medicine, Washington, D. C.

Dr. John A. Kolmer (Fellow), Professor of Medicine at Temple University School of Medicine, Philadelphia, Pa., was among those selected to conduct a graduate course in Medicine at the University of Florida, June 19th to 24th, under the sponsorship of the Florida Medical Association.

Dr. Tracey H. McCarley (Fellow), McAlester, Okla., has been elected President of the Oklahoma State Medical Association for 1933–1934.

OBITUARIES

DR. JOHN BLOSS WOLFE

Dr. John Bloss Wolfe (Fellow), Wilkes-Barre, Pa., died suddenly at his home on June 1, 1933, from angina pectoris.

Dr. Wolfe was born at Berwick, Pa., on March 21, 1892. He graduated from the Jefferson Medical College of Philadelphia in 1915 and was Resident Physician at the Episcopal Hospital, Philadelphia, for two years. He was also Resident Physician for several months at the Kensington Hospital of Philadelphia, but entered the military service during the War and was attached to Base Hospital No. 34; he was honorably discharged with the rank of Captain. In 1921, he became a member of the Staff of the Wilkes-Barre General Hospital, and at the time of his death was an Associate in Medicine.

Dr. Wolfe was active in all forms of medical work as well as civic affairs. He was a member and the Editor of the Bulletin of the Luzerne County Medical Society, a member of the Lehigh Medical Association, a member of the Pennsylvania State Medical Society and a Fellow of the American Medical Association.

He was a lover of the outdoors and very fond of playing golf. He made many trips into the most remote wildernesses of Northern Canada, hunting big game. He leaves a wife and four children, three boys and one girl.

In the death of Dr. Wolfe, the medical profession has lost a dear friend and able member; the community, one of its best physicians; and his family, a loving husband and father.

(Furnished by
G. E. BAKER, M.D., F.A.C.P.,
Wilkes-Barre, Pa.)

DR. WALKER EUGENE STALLINGS

Dr. Walker Eugene Stallings, an Associate of the American College of Physicians, died May 6th, at the Fitzsimons General Hospital, Denver, Colo.

Dr. Stallings was born at Newport, Ark., February 1, 1896. He attended Valparaiso University one year, Texas Christian University one year and then entered Vanderbilt University School of Medicine, from which he received his medical degree in 1920. He spent one year as an interne at the St. Vincent's Infirmary, Little Rock, Ark., and four additional months at St. Joseph's Infirmary, Memphis, Tenn. At a later date he pursued postgraduate study in tuberculosis and electrocardiography at the Fitzsimons General Hospital. On July 1, 1929, he entered the service of the U. S. Veterans' Administration as Tuberculosis Specialist at the U. S. Veterans' Hospital in Boise, Idaho. He also acted as Consultant in Tuberculosis to the St. Luke's Hospital at Boise and Consultant in Tuberculosis for the State of Idaho, and was in charge of the State Hospital for Tuberculosis.

Dr. Stallings was a member of the Idaho State Medical Society, the American Medical Association, the Southern Medical Association and the Denver Sanatorium Association. He became an Associate of the American College of Physicians during 1932.

Dr. Stallings' professional standing and ethics were of the highest and he was blessed with a delightful personality.